THE RELATIONSHIP OF PSYCHOLOGICAL STATE TO TRYPTOPHAN ADMINISTRATION IN HUMANS

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ABSTRACT

This thesis reports on an investigation of the relationship between administration of the amino acid, l-tryptophan and measures of psychological state in normal and depressed individuals. L-Tryptophan was administered in doses from 2 to 6 grams/day to twelve normal and eight depressed subjects for one to four weeks. This condition was compared with placebo and baseline phases within individuals. Mood state was monitored twice daily across all experimental phases by a series of 16 Visual Analogue Mood Scales (Norris, 1971) which condensed to three principal factors, labelled: alertness, contentedness and calmness. Side effects were also checked on a daily basis. Weekly ratings for the Zung depression Scale (Zung, 1965), State Anxiety Scale (Spielberger, 1970) and the Hopkin's Symptom Check List (Derogatis, 1974) were obtained throughout the trial for all subjects. Consideration of antidepressant effects was limited to depressed subjects. There was a lack of dramatic or consistent psychological effects for tryptophan relative to placebo or baseline phases within all subjects. Slight effects were limited to a reduction in alertness for four subjects and an increase in contentedness for two further individuals, one of whom was depressed. However, in no case were effects considered to be of general psychological or specific therapeutic significance. A notable increase in the severity and variety of side effects was apparent for nine out of twenty subjects. L-tryptophan is considered to have potential therapeutic relevance in biochmemically and/or psychologically select individuals. A function for l-tryptophan as an agent in the investigation of brain serotonergic function is also proposed.

CHAPTER I

INTRODUCTION

L-Tryptophan may be classed as a nutritionally essential amino acid in humans. The relevance of this compound to psychological state stems from its physiological role as a precursor to the brain amine, serotonin. Alterations in brain serotonin activity have been associated with a wide range of psychological states including depression (Coppen & Wood, 1983; Asberg & Traskman, 1981; van Praag & Korf, 1970; McGeer et al., 1978; Banki et al, 1981(a); (b)). The theoretical and empirical evidence relating serotonin metabolism to states of depression is evaluated in Chapter II. Motivation for psychological investigations of tryptophan administration relate to its assumed ability to increase the functional turnover of brain serotonin. Evidence bearing on this assumption is also presented in Chapter II. The desirability of establishing a therapeutic role for a physiologically natural substance represents another motivation for psychological investigation of l-tryptophan.

Lehman (1978) has proposed a set of criteria for the type of drugs psychiatrists might hope for in the future as well as those which psychopharmacologists should be testing clinically:

" 1. Greater therapeutic efficacy than existing drugs for the same indication
2. Lower toxicity
3. Fewer or less disturbing side effects
4. More desirable pharmacokinetic features
5. Different action mechanisms
6. A basically different chemical structure

psychopathological aspects of the condition that is being treated"

With respect to the above points, the therapeutic efficacy and pharmacokinetic desirability of tryptophan, relative to existing drugs, remains to be determined. However, it seems

reasonable to expect that a normal physiological compound will be characterized by lower toxicity and fewer side effects than non physiological drugs. L-Tryptophan also appears to have a more specific brain action - that of increasing serotonin synthesis - than other antidepressant drugs. This last factor indicates a value for tryptophan in investigating the 'serotonin depletion' hypotheses of depression (Carroll, 1971), and is further discussed in Chapters II and IV.

L-Tryptophan is presently available in New Zealand through Health Food Distributer's and has received compelling advertisements from such sources. For example, comments appearing in the Christchurch Shopping Guide (1983, 1984) read as follows.

"L-Tryptophan can virtually wipe out depression, anxiety and sleep problems for millions ... it can calm you down when your'e nervous or suffering stress, perk you up when you're blue and help you sleep like a baby"

In contrast, evidence considered in the present thesis for l-tryptophan's mood altering potential is injected with controversy. Reports of antidepressant efficacy range from no better than placebo (Bunney et al., 1971; Murphy et al., 1974; Mendels et al., 1975; Farkas et al., 1976; Cooper & Datta, 1980) to effects comparable with ECT (Coppen et al., 1967).

The mood altering effects of tryptophan in normal (non depressed) subjects has received little investigation to date. The present study addresses relationships between l-tryptophan administration and psychological state in normal as well as depressed individuals. Most past investigations of l-tryptophan's antidepressant effects have been based on the criterion of significant group differences between tryptophan and alternative treatments ranging from placebo to tricyclics or ECT. Such approaches have overlooked the possibility that tryptophan's therapeutic potential is limited to psychologically and/or biochemically select individuals. The present thesis is concerned with the need for evaluating l-tryptophan's efficacy within individuals. This approach characterizes the present

experiment (Chapters III and IV) and recommendations for future research (Chapter V).

The empirical part of the present thesis is concerned with investigating relationships between administration of l-tryptophan and self assessments of select aspects of psychological state in both normal and depressed individuals. By extending consideration to past investigations, attempts are made to evaluate tryptophan's psychological effects - particularly its therapeutic potential. Finally, tryptophan's value as as an agent in the investigation of serotonergic functioning is considered. Clearly, motivation for all aspects of the above inquiry rest on certain assumptions relating to the biological basis of behaviour.

The most pertinent assumption underlying the present experiment is that certain changes in psychological state, including antidepressant effects, may be correlated with administration of the serotonin precursor - tryptophan. Justification for this assumption is presented in the form of an evaluation of the psychological investigations of tryptophan administration in Chapter II. Much of the evidence in this area is focused on tryptophan's antidepressant potential. However, consideration is also given to tryptophan's hypnotic action and effects related to administration in normal (non psychiatric) individuals.

Subsequently, if specific and consistent effects such as an antidepressant response (in depressed subjects) can be demonstrated, then it is assumed that the most suitable theory of action mechanisms relates to the ability of l-tryptophan to effect an elevation in the functional turnover of brain serotonin. The biochemical pathway relevant to cerebral serotonin synthesis is presented in Chapter II. The assumed preferential relevance of this pathway over alternative catabolic courses, i.e. the psychological significance of serotonin metabolism is also discussed. The proposed mechanism of action (Figure 2-2) requires that certain metabolic conditions within and between plasma and brain environments are established. The relevance of such conditions to psychological state (i.e. 1.

plasma - psychological 2. brain - psychological) and to each other (i.e. plasma - brain) are presented and evaluated in Chapter II. As indicated from this evaluation, such information is of value in reducing the conflict emanating from purely psychological investigations and argues in favour of biochemical screening and monitoring of subjects particularly in the therapeutic context.

Assumptions regarding the psychological status of participants in the present study require justification. As already mentioned part of the present thesis is concerned with the evaluation of tryptophan's antidepressant potential. As indicated from Chapter IV, only eight of the twenty participants could be considered depressed on the basis of 'motivation for participation' and only five of these eight on the basis of initial SDS (Zung Depression) scores. Consequently, evaluation of l-tryptophan's antidepressant effects was limited to these individuals. It was not assumed that non depressed participants would act as models for the antidepressant action of tryptophan. However, the use of scales (particularly the VAMS) which had demonstrated sensitivity within both normal and depressed/anxious subjects allowed exploration of a response continuum between these two groups.

Prior to commencement of the present experiment, the author experienced all of the tasks required of subjects. The experimental conditions were the same as those described for subject 01 (Chapter IV). This procedure involved the maximum dose of tryptophan as well as the maximum length of participation. Analysis of the author's trial was not included in this thesis. However, the experience proved useful in that it led to certain design modifications prior to the start of the main experiment.

All references to 'tryptophan' in the present thesis are synonomous with 'l-tryptophan' unless otherwise stated. The significance of l and d isomers is discussed in Chapter II.

CHAPTER II

PSYCHOBIOLOGY OF TRYPTOPHAN

2.1 INTRODUCTION

This chapter provides a description and evaluation of the psychobiological relationships of tryptophan in humans. The evidence considered provides background information relevant to the design and outcome of the present experiment. Consideration is also given to areas beyond the boundaries of the present investigation, in order that a broader based evaluation of tryptophan's therapeutic and general mood altering potential may be formulated.

Initial consideration is given to evidence emerging from purely psychological investigations of tryptophan administration in depressed and normal individuals. Studies in this context ignore the pharmacological sequences hypothesized to intervene between tryptophan ingestion and altered psychological state (Figure 2-2). Thus, such investigations are considered to contribute a low level of information towards understanding of the psychobiological relationships of tryptophan administration. Outcome from studies in this context is typified by conflict with respect to both general mood altering properties and therapeutic efficacy.

While some of the conflict from psychological investigations of tryptophan administration is considered attributable to various design differences and inadequacies, it is proposed that additional areas of controversy may be reduced through knowledge of basic biochemical and metabolic processes of the amino acid and the relationships of these processes to tryptophan intake and psychological state. Consequently consideration is given to the basic structural, biochemical and metabolic features of tryptophan and subsequently the psychophysiological and psychopharmacological relationships relevant to depression and normal psychological functioning.

2.2 PSYCHOLOGICAL STUDIES

The majority of information in this context relates to the antidepressant effects of tryptophan administration. Consideration is also given to the general mood altering effects associated with tryptophan intake in normal subjects.

2.2.1 Antidepressant trials

The motivation for antidepressant applications of tryptophan stems from information relating to two major areas of research to be described in following sections of this chapter. Firstly comparative biochemical investigations of depressed and normal subjects have indicated differences relating to tryptophan and serotonin metabolism. The implication from such findings is that certain types of depression may be characterized by functional abnormalities in these systems. The second line of evidence relates to the demonstration that administration of tryptophan to certain depressives correlates with antidepressant response and certain specific changes in metabolic parameters of tryptophan.

2.2.1.1 Tryptophan versus standard tricyclics

Nine studies were considered in the evaluation of tryptophan's therapeutic efficacy relative to standard tricyclics. The description and basic outcome emerging from such studies is presented in Table 2-1. The six studies in this context comparing tryptophan with imipramine and the two with amitriptyline resulted in positive outcomes. That is, in all the above eight cases tryptophan was considered as efficacious as the tricyclics in the treatment of depression. The investigation indicating superiority of tricyclics over tryptophan varied in two important respects from the remaining studies. Firstly, trytophan was compared with clomipramine and doxepin and secondly, the tryptophan dose employed was half that of the lowest dose used in the positive studies.

These studies indicate tryptophan may be as efficacious in the treatment of depression as imipramine and amitriptyline. This indication is further endorsed by the fact that most of the

Table 2-1 Studies comparing the antidepressant efficacy of tryptophan with tricyclics: imipramine, amitriptyline, clomipramine and doxepin

Authors	Psychological status of subjects	Design	Dose (gms/day)	Duration (days)	Outcome
Chouinard et al (1979)	"primary affective disorder"(Feighner,1972) initial mean HDS scores: tryptophan= ~ 41 imipramine= ~ 38	tryp n=8 imip n=8	4-6	28	tryptophan as effective as imipramine
Coppen et al (1972)	"primary depression" (Kline,1961) initial mean HDS scores: tryptophan= 23.5 imipramine= 23.4	tryp n=15 imip n=15	9	28	trytophan as effective as imipramine
Herrington et al (1976)	"primary depression" (MRC criteria, 1965) initial mean HDS scores: tryptophan= ~ 24 amitriptyline= ~ 22	tryp n=20 amit n=20	6-8	28	tryptophan as effective as amitriptyline
Jensen et al (1975)	"endogenous depression" (unspecified criteria) initial mean HDS scores: tryptophan= 25.6 imipramine= 23.9	tryp n=22 imip n=20	3-6	21	tryptophan as effective as imipramine
Kline & Shah (1974)	"active depressive illness"(unspecified criteria)	tryp n=17 imip n=17	3-6	42	tryptophan as effective as imipramine
Lindberg et al (1979)	"38 endogenous inpatients and 20 non-endogenous inpatients"(unspecified criteria)	tryp n=29 imip n=29	3-6	21	tryptophan as effective as imipramine
Linnoila et al (1980)	"primary depression" (unspecified criteria) initial mean HDS scores: tryptophan= ~ 26 clomipramine= ~ 27 doxepin= ~ 25.5	tryp n=16 clom n=13 doxp n=13	1.5	21	clomipramine and doxepin superior to tryptophan
Rao & Broadhurst (1976)	"depressive illness" (Clinical Psychiatric Committee, 1965) initial mean HDS scores: tryptophan= 25.33 imipramine= 22.86	tryp n=9 imip n=7	6	28	tryptophan as effective as imipramine
Thomson et al (1982)	"outpatients complaining depression at least 2 weeks" initial mean HDS scores: tryptophan= 18.21 amitriptyline= 17.35	tryp n=29 amit n=31	3	60	tryptophan considered as satisfactory alternative to amitriptyline

HDS Hamilton depression scale total score (Hamilton, 1965)
~ approximate score ie: interpreted from graphic displays
tryp =tryptophan imip =imipramine clom clomipramine
doxp =doxepin

above studies involved randomized, double blind experimental procedures. All the studies were considered to have run for sufficient duration. Although 28 days is generally regarded as a minimum fair test of an antidepressant (Cooper & Sudhir, 1980), Wittenborn (1978) suggests three weeks should generally be sufficient for tests of antidepressant efficacy. Most studies, with the possible exception of Chouinard et al. (1979) and Rao & Broadhurst (1976), could be considered to have involved comparison of sufficiently large groups in either condition.

However, there do remain some methodological and design procedures which could be considered to detract from the validity of indivivdual studies. Firstly, all the studies cited in Table 2-1 were based on group comparative approaches. Discussion relating to the inadequacy of this design is presented in Chapter III. In general, the problem here is considered to relate to the potential inaccuracy of evaluations based on a group response. In the case of the above investigations it may only take a few dramatic/extreme individual reactions to shift a 'group response' away from an outcome which is representative of most of the individuals. There was little evidence in the above investigations that attention had been paid to individual effects. In this respect, Kellner et al. (1978) note that, "a drug trial with a group ... is more likely to yeild statistically significant drug/placebo differences than an intensive design with a single case".

A second methodological aspect of the above investigations which demands consideration concerns the psychological status of the groups and individuals studied. As is evident from Table 2-1, classification was often limited to global statements such as 'primary affective disorder', 'primary depressive disorder' and 'endogenous depression'. In some cases criteria for such judgements conformed to standard nosological systems and in other cases they were unspecified. Such variation hinders comparison of the above investigations and in some cases leads to uncertainty over the type of depressions being considered.

As indicated in Table 2-1, seven of the nine studies considered supplied information on the severity of depression in

the form of mean Hamilton Depression Scale (HDS) scores. On this basis most investigations could be considered to have involved subjects with moderate levels of depression. Finally, it should be noted that three of the studies considered here employed concurrent administration of pyridoxine (vitamin B6) with tryptophan. However, the procedure did not appear to be significantly associated with therapeutic outcome.

Studies comparing tryptophan with the tricyclics seem pertinent in establishing tryptophan's antidepressant utility at a fairly rigorous level. That is, James et al. (1976) consider tricyclics to be the drugs of choice in depressive illness, presumably because of their relatively frequent utilization and wide ranging efficacy. Thus, demonstration of a drug's antidepressant efficacy equal to that of the tricyclics should endorse its potential therapeutic value. However, studies comparing tryptophan with ECT and placebo are less positive.

2.2.1.2 Tryptophan versus ECT

Experimental details for the three studies considered in this section are documented in Table 2-2. Clearly, such investigations are precluded from conformation to double blind standards. That is, the disparities in administrative procedures between tryptophan and ECT are unlikely to keep either the dispenser of therapies or the recipient in ignorance of treatment differences.

As is evident from Table 2-2, two of the three studies (Carroll et al., 1970 & Herrington et al., 1974) found tryptophan to be significantly less effective than ECT in treatment of severe depression, while Coppen et al.'s (1967) results suggest that tryptophan was as effective as ECT. All studies involved severely depressed inpatients, although the criteria for classification were not clearly specified in any case.

Coppen et al.'s (1967) study was the only one not to employ random assignment procedures. However this feature alone seems insufficient to account for the difference in outcome relative to the other two trials. All studies employed concomitant

Table 2-2 Studies comparing the antidepressant efficacy of tryptophan with ECT

Author	Psychological status of subjects	Design	Dose (gms/day)	Duration (days)	Outcome
Carroll et al (1970)	severe depression (criteria unspecified) initial mean HDS total: tryptophan = 26.3 ECT = 26.6 all patients considered to require ECT	tryp n=12 ECT n=12	7	21 3 ECT/week	Criteria for antidepressant efficacy required reduction of 8 pts on HDS. Final HDS mean total: tryptophan = 21.0 ECT = 11.6 Thus, tryptophan considered ineffective. All ECT patients improved rapidly in 3 weeks, 1 tryptophan patient was symptom free, 2 improved & 3 worse.
Coppen et al (1967)	severe depression, mean inital beck dep score: tryptophan = 21.9 ECT = 22.2 all patients considered to require ECT	tryp n=22 ECT n=36	5-7dl	28 2 ECT/week	no sig. difference in depression self ratings at completion, 22% ECT group & 16% tryptophan group required further treatment prior to discharge.
Herrington et al (1974)	severe depression,initial mean HDS total: tryptophan = ~26 ECT = ~26.5	tryp n=22 ECT n=21	6-8	28 2 ECT/week	Authors conclude ECT superior to tryptophan & consider it unlikely that tryptophan has a function in the treatment of patients considered to require ECT. Final HDS totals: no sig diff at 2 weeks but at 4 weeks tryptophan = ~15 ECT = ~5 i.e. ECT mean HDS sig lower.

administration of 100mg of pyridoxine with tryptophan and in all cases the duration of application was considered sufficient, in the light of Wittenborn's (1978) recommendations. The lower dose in Coppen et al.'s (1967) does not provide an adequate explanation of outcome difference. While it is possible that the ability to accomplish accurate self ratings (the method of assessment used in Coppen et al.'s (1967) study) may be impaired in severely depressed patients, claims for tryptophan's effectiveness were not entirely dependent on such criteria. The outcome from this study was also supported by the finding that only 16% of the tryptophan group (compared to 22% of the ECT group) required further treatment prior to discharge.

Finally, an important factor emerging from Herrington et al.'s (1974) trial relates to the elevation in tryptophan dose at the second week of administration. This intervention coincided with a seperation in therapeutic effect between the ECT and tryptophan groups. That is, up to the end of the second week there was no significant difference between the groups on HDS. Following this point the ECT group continued to improve while mean ratings from the tryptophan group stabilized, such that by completion of the fourth week the difference was signifcant, in favour of ECT. Evidence emerging from Chouinard et al.'s (1978) investigation of appropriate dose ranges would suggest that 8gms/day (the dose for the last two weeks of Herrington et al.'s (1974) trial) is in excess of optimum levels and could be expected to relate to therapeutic decline.

Although two of the above studies indicated tryptophan was inferior to ECT, such information does not in itself justify supposition that tryptophan is inadequate as an antidepressant. Both studies indicated notable declines in mean HDS scores for the tryptophan condition. In addition, the coincidence of change in dosage with reduction in the rate of therapeutic improvement for Herrington et al.'s (1974) tryptophan group limits the validity of this trial. Clearly, the above evidence is insufficient to allow definitive judgement of tryptophan's potential rating against ECT - a therapeutically potent aprroach to treatment of severe depression. However, the demonstration of some antidepressant effect for tryptophan, in

all of the above studies is supportive of the need for further investigation of its efficacy.

2.2.1.3 Tryptophan versus placebo

The studies considered in this section are outlined in Table 2-3. An inherent assumption of most investigations comparing the antidepressant efficacy of tryptophan with the tricyclics seems to be that administration of the latter compounds are exerting effects superior to placebo. However, trials indicating tryptophan's equality or superiority relative to the tricyclics are not necessarily sufficient to determine whether tryptophan's psychological effects have a true pharmacological base. There is a need to demonstrate tryptophan's efficacy relative to placebo before significant pharmacological effects can be assumed. Unfortunately there is an absence of studies involving concurrent comparison of tryptophan, placebo and antidepressants such as the tricyclics and ECT. However, studies comparing tryptophan with placebo are considered in this section.

Although the severity of depressions considered in these trials is not always stated, there were general indications from some that only subjects with mild to moderate depression were accepted, e.g. minimum HDS inclusion scores of 12 and 16 were set by Thomson et al. (1982) and Farkas et al. (1976) respectively. The ethical problems associated with administering placebo to depressed patients is also likely to have resulted in inclusion of less severely depressed patients than for studies comparing tryptophan with the tricyclics. As evident from Table 2-3, all studies employed double blind procedures. Three of the six investigations involved cross over of conditions within subjects, considered by the present author to represent a more valid comparison of effects than between group evaluations. At least four of the studies were considered to involve adequate trial lengths for detection of antidepressant effects. However, in four of the studies dose levels could be considered to exceed therapeutically optimal levels according to Chouinard et al.'s (1978) recommendations.

Table 2-3 Studies comparing the antidepressant efficacy of tryptophan with placebo

Author	Psychological status of subjects	Design	Duration (days)	Dose (gms/day)	Outcome
Bunney et al, 1971.	manic depressive & psychotic depression	double blind crossover. random assign. n=8	16	8	no sig diff for tryptophan relative to placebo & no sig antidep. resp from tryptophan
Murphy et al, 1974	primary affective disorder, 16 unipolar, 8 bipolar.	double blind, non random crossover.	20 +/-2	9.6 + ascorbic acid & pyridoxine	no sig diff for tryptophan relative to placebo, 1/16 unipolars - sig improv & 5/8 bipolars - sig reduction of manic symptoms with tryptophan
Mendels et al, 1975	Unipolar & bipolar dep, min HDS of 16 required for inclusion, therefore, not severe dep	double blind tryptophan n=6 placebo n=3	42	max range 11-16 + pyridoxine	no sig diff for tryptophan relative to placebo. No sig improvemnent with tryptophan or placebo but antidep trends for both
Farkas et al, 1976(includes results from Dunner & Fieve, 1975	primary affective dis, (criteria of Feighner, 1972). 10=unipolar, 6=bipolar.	double blind crossover	placebo 3-7 days, tryp 10-18 days	9 + pyridoxine	no sig diff for tryptophan relative to placebo. Sig antidep resp 1/10 unipolar & 3/6 bipolar on tryptophan
Cooper & Datta, 1980	mild to mod depress, (criteria unspecified) mean age approx 80yrs	double blind random assign tryptophan n=20 placebo n=20	42	6 + pyridoxine & ascorbic acid	no sig diff for tryptophan relative to placebo. Trends apparent for antidepressant resp on both tryp and placebo
Thomson et el, 1982	general practise patients complaining of depression for at least two weeks. Most met the criteria for primary affective disorder (Spitzer et al, 1977)	double blind, random assigm one week placebo foll by compar of 1.n=29 tryptophan 2.n=28 placebo	84	3	tryptophan sig greater response than placebo. Placebo also associated with notable improvement

Given the above limitations, there is still concensus between studies that the antidepressant effects of tryptophan are not significantly different from placebo. Five out of six studies were in agreement in this respect. In the study indicating tryptophan's superiority to placebo the difference was only significant at the 0.05 level. The above outcome indicates the need for a re-examination of the meaning of results demonstrating comparable efficacy of tryptophan relative to the tricyclics. It should be noted that although there was a general lack of antidepressant difference for tryptophan versus placebo, that placebo administration was clearly related to antidepressant effects (Cooper & Datta, 1980; Thomson et al., 1982; Mendels et al., 1975), as evidenced by marked declines in HDS scores in this condition. Unfortunately, the authors did not comment on the significance of such effects.

Thus, while tryptophan appears to be comparable in efficacy to standard tricyclics, the present results indicate the need for demonstration of tryptophan's effects relative to placebo and tricyclics within the same study and preferably within individuals before it can be assumed the psychology of tryptophan administration involves more than placebo effects.

2.2.1.4 Tryptophan's potentiating power

(a) With tricyclics

As indicated in Table 2-4, three studies are considered which involve comparison of tryptophan administered concurrently with amitriptyline and clomipramine versus the latter compounds alone. All studies were considered to run for a reasonable trial period. Each study employed an effective dose of approximately 3gms/day tryptophan in conjunction with therapeutic tricyclic doses. That is, the dose levels of tricyclics alone, led to significant antidepressant respones in all cases. As evident from Table 2-4, the addition of tryptophan to an amitriptyline regime in the first study (Lopez-Ibor Alino et al., 1973), was not considered to potentiate the antidepressant response. Although not significant, there was a noticeable decline in depression scores for the combination relative to amitriptyline

Table 2-4 Studies comparing tryptophan's potentiating influence with the tricyclics

Author	Psychological status of subjects	Design	Duration (days)	Dose (gms/day)	Outcome
Lopez-Ibor Alino et al, 1973	Inpatients with mod-severe depression	double blind amitryptyline n=15 tryptophan n=15	30	3	no overall sig diff betw tryp & amitryp + tryp, although tryp comb showed slightly greater reduc in symps relative to amitryp
Thomson et al, 1982	genaral practise patients complaining of deprss at least 2 weeks - most met criteria for primary affec. dis (Spitzer, 1977)	double blind, random assign all subjects 1 week placebo foll by compar of: 1. n=28 placebo 2. n=31 amitryp 3. n=29 tryp 4. n=27 amit+tryp	84	3	while all three trts sig greater placebo. Comb sig superior in relieving depr mood than either alone
Walinder et al, 1976	inpatients with endog depress	double blind, random assign n=12 tryp + clomipramine n=12 placebo + clomipramine	21	dl tryp used, effcv (1) dose ~3gms	significantly greater antidp effect apparent for clom+tryp group at 12 days relative to clom+placebo

alone. The same study also demonstrated a significant increase in side effects with the combination treatment. Similarly in Thomson et al's (1982) investgation, although there was no overall reduction in the HDS total score for the combined administration relative to amitriptyline alone, a significant reduction was noted for symptoms relevant to depressed mood. Thus, there is evidence that addition of 3gms/day tryptophan to 150mg/day amitriptyline may result in slight increases in therapeutic response relative to tryptophan alone. In the case of clomipramine, the authors (Walinder et al., 1976) claimed that addition of tryptophan led to a significantly greater and more rapid antidepressant response relative to clomipramine alone.

The finding of slight to significant improvement for tryptophan + the tricylclics relative to the tricyclics alone, indicates a potential role for tryptophan in this therapeutic context. However, investigaton within individuals and exploration of dose variations as well as side effect incidence is required before its value is established.

(b) With ECT

Studies considered in this context are described in Table 2-5. Clearly, all subjects in such studies could be considered severely depressed. The two most comparable investigations indicated no potentiation of ECT by the addition of tryptophan, relative to the addition of saline or placebo (Kirkegaard et al., 1978) and (d'Elia et al., 1977) respectively. A major drawback to investigation in both these cases was the lack of within subject monitoring. Also, the commencement of tryptophan administration occurred just prior to the first ECT, thus, in some cases tryptophan may have been consumed for an insufficient period to prior to therapeutic remission. In the case of Kirkegaard et al.'s (1978) investigation, a dose of 10mg/kg would seem therapeutically inadequate in the light of Chouinard et al's (1978) recommendations.

The final study considered in this section concerns a single case. The positive response claimed for tryptophan + ECT + amitryptyline relative to ECT or tricyclics alone indicates the

Table 2-5 Studies comparing tryptophan's potentiating influence with ECT

Author	Psychological status of subjects	Design	Duration (days)	Dose (per day)	Outcome
Kirkegaard et al, 1978	endog depression n=5 unipolar, n=2 bipolar, n=13 indefinite	double blind, random assign, n=10 tryp+ECT n=10 saline+ECT	ave 35	~10mg/kg	no sig diff betw groups in level/rate of improvement
d'Elia et al, 1977	severe depression several subjects demonstr previous resistance to drugs eg:amitryptylene	double blind, random assign, n=30 ECT+plac n=31 ECT+tryp tryp admin began 1 day prior ECT	10-43	6gms + pyridoxine	no diff in recov betw ECT+tryp & ECT+plac
Rao, 1972	severe depression resistant previous treatments	single case clinical compar of amitrip, ECT, amitrip+ECT & amitrip+ECT+tryp	unstated	7gms + pyridoxine	marked improvement noted after addition 7gms/day tryp to ECT+amitrip. Response maintained on amitrip+tryp

Table 2-6 Studies comparing tryptophan's potentiating influence with MAOI's

Author	Psychological status of subjects	Design	Duration (days)	Dose (gms/day)	Outcome
Coppen et al, 1963	severe depression	double blind, random assign, n=12 tryp+MAOI n=13 MAOI	7	dl tryp, effec l dose ~ 5-8 + pyridoxine	tryp+MAOI gave sig greater improvement than MAOI alone
Coppen et al, 1967	severe depression	single blind, n=19 tryp+MAOI n=22 tryp	28	dl tryp, effcv (1) dose ~2-4gms + pyridoxine	some incr in response for tryp+MAOI compared tryp alone but tryp alone also gave a sig antidep response
Glassman & Platman,1969	severe depression	double blind, n=10 tryp n=10 tryp+MAOI	21	dl tryp, effcv dose ~ 6-9gms (1)	sig greater improvement from MAOI+tryp than MAOI alone
Gutierrez & Lopez-Ibor Alino, 1971	severe endog dep	double blind, random assign, n=14 tryp+MAOI n=15 plac+MAOI	20	6gms dl tryp ~ 3 (1)	sig greater improvement for tryp +MAOI relative to MAOI+placebo, onset of effect much more rapid for tryp+MAOI than MAOI+placebo
Pare, 1963	depressed patients who prev responded to various MAOI's and showed subseq relapses	double blind, random assign, crossover	>10	7.5-15	6/14 sig improvement after 3-4 days of tryp addition to MAOI, and all relapsed when tryp replaced by placebo

need for further within subject comparisons before tryptophan's value as a potentiator of ECT is dismissed.

(c) With MAOI's

The information considered here offers greater consistency with respect to the potentiating role of tryptophan. As indicated in Table 2-6, four of the five studies considered indicated significant improvement for an MAOI+tryptophan relative to an MAOI alone. In all cases significant response was obtained by MAOI's alone, indicating that dose levels of these compounds were therapeutically adequate without addition of tryptophan. The remaining study considered in this section actually involved comparison of an MAOI+tryptophan with tryptophan alone. In this case the combination was noted to be more effective than tryptophan alone but not significantly so.

While variability in factors such as dose level and administration length was apparent across the above studies, there are reasonable theoretical grounds for expecting an improvement in antidepressant effect from concomitant administration of an MAOI and tryptophan, than either compound alone. That is, the main focus of MAOI action is to impede deamination of 5HT. While tryptophan administration alone, may be expected to increase serotonin synthesis, it can not be assumed that this action equates with increased functional serotonin activity. The the increase in 5HT synthesis following tryptophan administration may also lead to rapid breakdown of the amine to 5HIAA. The potentially synergistic psychological action of these componds, then, has biochemical support in that MAOI action may be expected to prolong the functional action of elevated 5HT levels induced through tryptophan administration.

2.2.2 Tryptophan's effects in normal subjects

The studies considered in this section are detailed in Table 2-7. It should be stated that 'normal' in this context refers to non psychiatric subjects - specifically free from depression. In addition, none of the studies considered in this context have employed normal subjects as models for antidepressant effects.

Table 2-7 Studies investigating the relationship between tryptophan administration and psychological state in normal subjects

Author	Sample	Design	Duration	Dose	Outcome
Charney et al, 1982.	n=4 male n=6 female	tryptophan cf placebo n=2, cf saline n=8 conditions sep by 3 weeks	single dose mood ratings at base,30,50,60,70, 90,120,180 mins foll infusion	intravenous 7gms	sig incr for tryptophan on: drowsiness by 75% for 9/10 lasting 2 hrs; mellow & high by 75% for 6/10. All sensations peaking at 30-50mins. Most subjects reported infusion to be pleasant experience. 4/10 mild to transient nausea during infusion, passed at 60mins. 5/10 lightheadedness
Yuwiler et al, 1981.	n=5 males	tryptophan administered in drinking chocolate cf to tryptophan alone	(i)single dose and 6 hr foll up (ii)14 days	oral (i)50 & 100mg/kg (ii)50mg/kg	(i)drowsiness: 20-30 min foll admin, lasting 2-4 hours; nausea: 30min after admin, lasting up 3 hours. (ii)similar effects with lethargy often persisting into evening.
Greenwood et al, 1974.	n=6 males	2 doses tryptophan compared physiol saline	single dose mood ratings at one hour	intravenous 75 & 100mg/kg	sig increase for tryp vs saline (both doses)on VAMS dimensions:drowsy clumsy, bored, incompetent dreamy, mentally slow and lethargic and for 100mg/kg only: increase: relaxed and calm VAMS factors 'alertness' showed sig decrease, 'calmness' sig increase and no change in 'contentedness'.
Greenwood et al, 1975.	n=6 male n=4 female	tryptophan versus placbo - seperated by 10 days	single dose, mood ratings at hourly intervals over 3 hours	oral 5gms	sig increase for tryp vs placebo on:drowsiness, clumsiness, muzziness and mentally slow as measured by VAMS - used in present study. Freq reports nausea for at least half subjects 10-30mins foll admin and incr headache during 2nd hour.
Smith & Prockop, 1962	n=5 male n=2 female	tryptophan in apple sauce cf applesauce alone	single doses, monitered over 3 hours	30,50,70 and 90mg/kg on sucessive days	5/7 complained drowsiness 1-2 hours foll 30 & 70mg/kg. All subjects became listless & yawned freq foll 90

Rather, the focus of such investigations has been the detection of general mood altering effects and side effects associated with tryptophan ingestion.

As is apparent from Table 2-7, most studies involved investigation of acute tryptophan doses and monitoring of psychological states from one to three hours following administration. In this respect such studies deviate considerably from the focus of trials investigating antidepressant effects and also from the longitudinal approach to the investigation of general mood altering effects employed in the present thesis. Most studies employed relatively high dose levels, in keeping with quantities employed by therapeutic investigations.

The main significant effect reported by all the investigations in Table 2-7, was 'drowsiness'. Other effects common to most studies concerned similar reactions described as 'lethergy', 'lightheadedness' or 'mentally slow'. The only other common effect within and across studies concerned reports of nausea which generally only lasted from 1/2 to 1 hour. Finally two of the five studies noted significant increases in euphoric effects.

Thus, it is difficult to establish whether limitation of reports to a few negative side effects is characteristic of tryptophan relationships in normal subjects as opposed to depressives, or rather a consequence of the focus of measuring reactions for only a short period following a single tryptophan administration. The possibility exists that normal subjects may be more oriented to the expectation of negative side effects as opposed to depressed individuals who may be more oriented towards expectations of therapeutic effects. This speculation is supported by findings that placebo administration resulted in significant increases in the incidence and severity of side effects in normal as opposed to depressed patients (Green,1964). There remains insufficient evidence to speculate on the dynamics of longterm tryptophan administration in normal subjects.

2.2.3 Effects on sleep

It is not intended to review the literature concerning tryptophan relationships to sleep in the present thesis. Various controversial claims relating to tryptophan's hypnotic properties have been made. Results for significant reductions in sleep latency i.e. the time taken to fall asleep have been repeatedly forwarded by Hartman et al. (1976, 1977 ,1981) and Hartman & Spinweber (1979). However, other studies have failed to support such claims (Adam & Oswald, 1979) and still others report an increase in the time to fall asleep (Gnirss et al., 1978). While some investigators have reported significant increases in total sleep time (Wyatt et al., 1970; Hartman et al., 1976), this parameter does not seem as pertinent as relationships to sleep latency and quotas of REM or slow wave sleep.

2.2.4 Value of psychological investigations of tryptophan administration

The conflict in outcome between studies in most of the above psychological contexts inhibits the formulation of generalizations regarding the psychological relevance of tryptophan. Results from studies considered in this section, investigating antidepressant efficacy, range from effects no better than placebo to levels of response exceeding ECT. While there are suggestions from most therapeutic applications that tryptophan has antidepressant properties, the lack of unanimity regarding the magnitude and specificity of effects indicates the need for more refined psychological investigation. Overall, the methodology employed by the majority of the above studies is considered inappropriate as a strategy for evaluation of tryptophan's therapeutic potential and, as indicated above, may be responsible for much of the conflict in outcome between investigations.

One of the main propositions to be developed within this thesis is that tryptophan's therapeutic value appears to be of relevance to biochemically and possibly psychologically select groups of depressives. Thus, even in studies where biochemical information is unavailable a more refined approach to the

evaluation of tryptophan's efficacy is indicated. Instead of the persistent investigation of group differences as a basis for setting tryptophan's value, a more selective focus on individual response is required. In addition, the need for a more specific qualification of the type of depressions and relationship to outcome is suggested.

The casual application of terms such as 'endogenous depression' by many of the above studies do not facilitate comparison, particularly when the criteria for such classifications are unspecified. This particular label appears to have evolved through a wide variety of semantic definitions. The original application of the term to psychology by Gillepsie (1929) referred to an emotional response to environmental changes which did not demand the presence of a precipitating event. Then, according to Katz & Hirchfeld (1978) endogenous depression became poised in contrast to neurotic/reactive depression. The more recent concept of endogeneity refers to the following behaviour/symptom oriented complex: "early morning waking, anorexia and weight loss, psychomotor disturbance, diurnal mood variation, severe depressed mood and lack of reactivity to environmental stimuli" (Katz & Hirchfeld, 1978). The foregoing variation in the meaning of this term raises uncertainty as to the present consistency of its semantic application, thus hindering comparison of investigations.

Two studies considered above (Murphy et al., 1974; Farkas et al., 1976) indicated significantly different therapeutic response between bipolar and unipolar classifications of depression. Thus, polarity of depression may provide a useful predictor for therapeutic response to tryptophan.

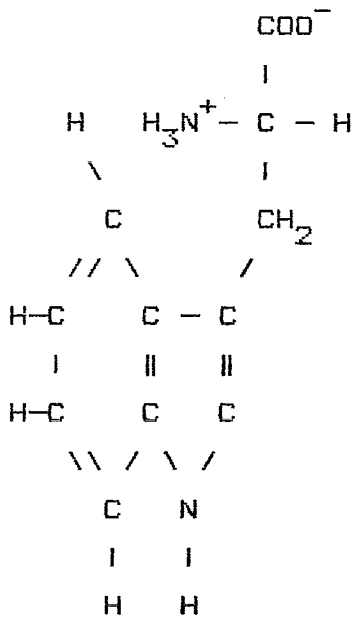
Overall the findings from psychological investigations are considered insufficient to match Wittenborn's (1978) guidelines for the utility of new drugs. There it is stated, "In general the case for a new psychotropic agent is strengthened if it exceeds placebo and also equals or exceeds a standard medication in two out of three studies". While the latter criterion has been met there is still insufficient evidence to establish tryptophan's value relative to placebo.

2.2 BIOCHEMISTRY AND METABOLISM OF TRYPTOPHAN

This section is devoted to an outline of tryptophan's structure, composition and biochemical properties along with a discussion of the catabolic pathways considered relevant to the present inquiry e.g. mood alteration and negative side effect experience.

For the purposes of the present thesis, classification of l-tryptophan as one of the eight to ten[1] nutritionally essential amino acids in man seems most pertinent. That is, l-tryptophan cannot be synthesized from the necessary precursor components within the human system and must be supplied through the diet. Proposed daily requirements range from 0.5 g/day (Rose et al., 1954) to more recent recommendations of 0.2 - 0.24 g/day (Lloyd et al., 1978 and Harper et al., 1977 respectively).

2.2.1 The molecular structure of tryptophan



molecluar weight ($C_{11}H_{12}N_2O_2$) = 204.23

1 Arginine & histidine are sometimes classed as semi-essential as they may be synthesized within human tissue but not in sufficient quantity to support growth in younger individuals (Harper et al., 1977).

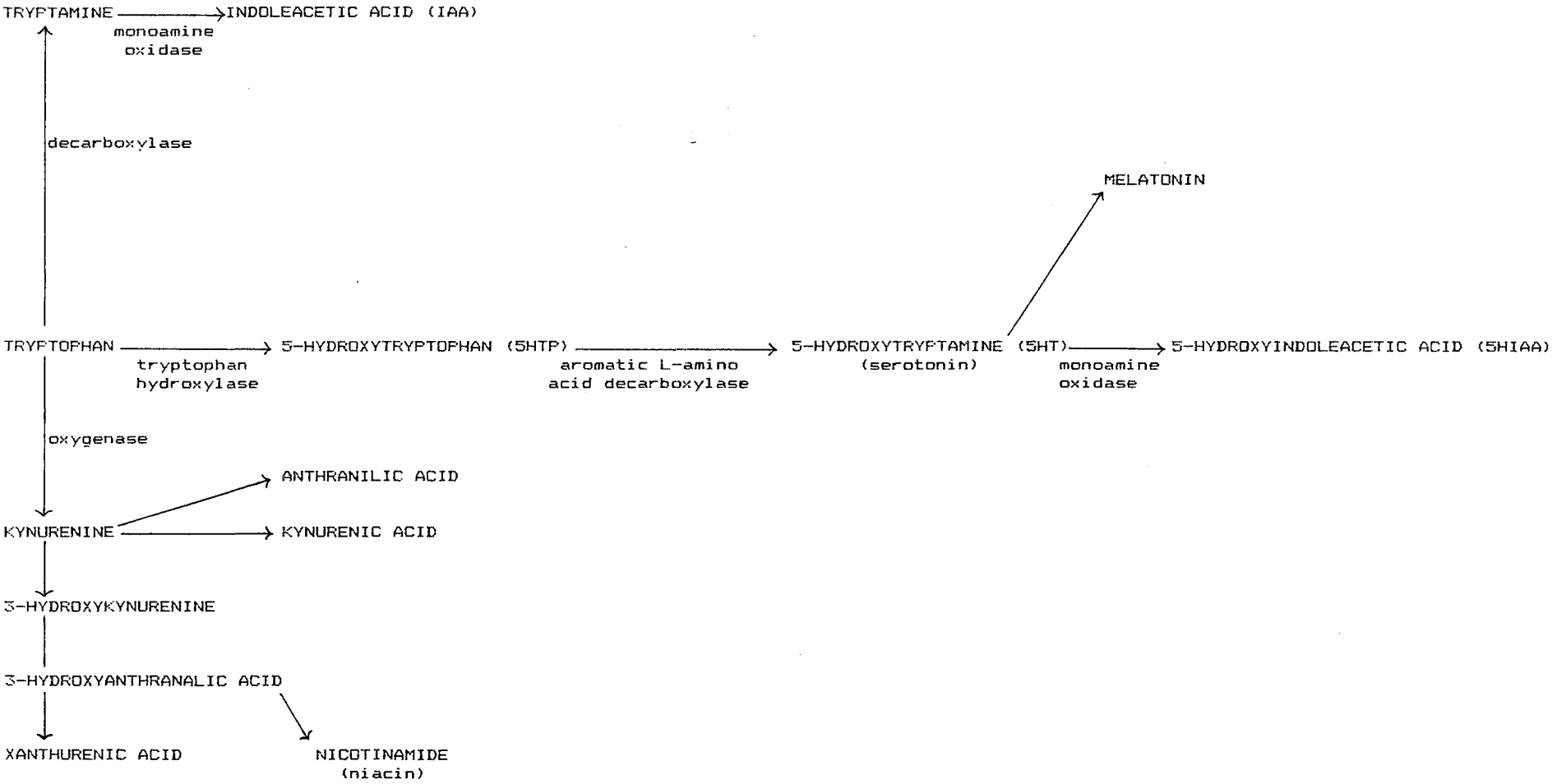
The structure is characterized by attachment of an indole ring to the basic amino acid complex. The single assymetric carbon atom determines the existence of two optically isomeric forms, i.e. (1) levorotary (l) rotates the polarized light plane to the left and (2) dextrorotary (d) to the right. D-amino acids do occur in cells and in polypeptides (Harper, 1977), however, the d seris are not incorporated into proteins and in the case of tryptophan the l and d isomers are metabolized by the human system to kynurenine but further catabolism only occurs with the l form. For the purposes of the present study, metabolism of d-tryptophan is considered to be psychologically irrelevant. With respect to the present thesis, administered tryptophan consisted only of the l isomer, similarly most references to past research are focused on the l form. Thus, reference to tryptophan from this point, unless otherwise stated, is synonymous with l-tryptophan.

2.2.2 Tryptophan metabolism

Illustration and description of the biosynthesis of tryptophan was ommited from this investigation, as the processes involved bear no direct relevance to the inquiry. Meister (1967) has traced the biosynthetic processes for tryptophan in detail.

Catabolism follows several courses on entry to the human system (see Figure 2-1). A large proportion of ingested tryptophan is utilized in the synthesis of tissue proteins (Harper et al., 1977; Lloyd et al., 1978) - the processes of which are ommitted from this discussion. The biological half-life of tryptophan has been determined at 15.84 hours in man (Ritschel, 1970). This index refers to the time required for half the amount of the drug absorbed to be eliminated, whether by excretion or catabolism, following establishment of equilibrium. This parameter is of relevance to therapeutic dose levels. As Ritschel (1970) notes, drugs with long half lives need to be administered at longer intervals relative to drugs with shorter biological half-lives in order to maintain therapeutic concentrations. Exact relationships between biological half life, required dose levels and frequency of administration are not given. However, the single daily tryptophan dose given in

Figure 2-1 BIOCHEMICAL PATHWAYS OF TRYPTOPHAN RELEVANT TO THE PRESENT THESIS



the present study can be more easily justified on the basis of a long biological half life relative to other common antidepressant drugs, e.g. imipramine = 3.5 hours.

2.2.2.1 The serotonin pathway

The pathway of direct relevance to the present study concerns the cerebral synthesis of serotonin (5HT). Approximately 1% of ingested tryptophan follows this course (Figure 2-1). The process involves oxidation of tryptophan to 5-hydroxytryptophan and decarboxylation of this amino acid to 5-hydroxytryptamine (serotonin). Serotonin is also synthesized in relatively high concentrations peripherally, that is, approximately 90% of the body's total concentration is detectable in the thrombocytes and argentaffine cells of the the intestinal wall. Its function here is uncertain but it may be implicated in the processes of peristalsis (Graham, 1979). Most of the remaining 5HT is distributed in the platelets (8%) and central nervous system (CNS) (2%). Within the CNS, 5HT cell bodies are almost exclusively located in the brainstem raphe nuclei (Aghajanian & Wang, 1978). Serotonin does not pass the blood-brain barrier to any significant degree[2] (Harper et al., 1977; Goodman et al., 1980) thus, for the purposes of the present investigation peripheral synthesis is considered to bear no significant relationship to brain synthesis or concentration.

Within the brain, tryptophan hydroxylase - the rate limiting step for 5HT synthesis - is generally agreed to be unsaturated with its substrate under normal physiological conditions (Eccleston et al., 1965; Friedman et al., 1972; Hamon & Glowinski 1974; Neckers et al., 1977), thus, the rate of brain 5HT synthesis should be effected by tryptophan supply among other variables. The importance of elevation in central serotonin synthesis (or rather functional turnover of this indoleamine) to psychological state will be explicated later in this chapter.

2 Goodman et al. (1980) note it is unusual to encounter central effects upon parenteral administration of 5HT.

2.2.2.2 The kynurenine - anthranilate pathway

The second relevant and quantitatively major degradative course, accounting for 98% (Hagen & Cohen, 1966) of tryptophan catabolism, is known as the 'kynnurenine-anthranilate' pathway. Here tryptophan is oxidized to kynurenine, which is converted to 3-hydroxyanthranilic acid, nicotinic acid (niacin) and other components in the liver. In man 60mg of tryptophan will lead to the production of approximately 1mg nicotinic acid (Harper et al., 1977). This pathway is of relevance in the therapeutic context to the extent that it may detract from central serotonin synthesis under elevated tryptophan conditions. That is, tryptophan pyrrolase (the rate limiting enzyme in this pathway) is inducible by its substrate i.e. tryptophan (Knox & Auerbach, 1955, Harper et al., 1977). This reasoning has led to investigation of the effects of concomitant administration of tryptophan pyrrolase inhibitors with therapeutic tryptophan doses (Green et al., 1980 (b)). The efficacy of this approach is considered in Chapter III, in relation to discussion of dose levels for the present experiment. The finding by Green & Curzon (1969) that hydrocortisone administration in rats led to an elevation of tryptophan pyrrolase activity as well as a reduction in brain 5HTP further suggests the significance of competition for tryptophan between the kynurenine anthranilate pathway and the central serotonin course.

The 'kynurenine-anthranilate' pathway is of relevance to the present investigation for two other reasons. This pathway is responsible for the production of niacin (vitamin B3). Niacin is conveniently used to cover the description of two compounds - nicotinic acid and nicotinamide. Nicotinic acid is easily converted to the physiologically active nicotinamide which functions metabolically as a component of two co-enzymes (NAD & NADP), (Pike & Brown, 1975). The widespread function of these co-enzymes in cellular metabolism (i.e. participation in over 40 different metabolic reactions involving electron transfer (Lloyd et al., 1978)) indicate a deficiency of the vitamin would have dramatic effects on cellular respiration. The well documented symptom profile resulting from niacin deficiency is termed pellagra. The condition includes skin lesions, diarrhea and

neurologic symptoms e.g. dementia (Goth, 1978). Tryptophan will normally contribute to the body's niacin supply given conditions such as an adequate supply of pyridoxine (vitamin B6) (Harper et al, 1977). A pellagrin state may, then, be a consequence of both tryptophan and niacin dietary deficiencies.

With respect to the present investigation and past trials involving the administration of therapeutic doses of tryptophan, it is probable that niacin levels will be significantly elevated. It is the potential consequence of this metabolic disturbance that is of relevance to the present inquiry. Niacin is able to pass the blood-brain barrier and may be subsequently effective in cerebral metabolism.

Application of niacin in the psychotherapeutic context marked the inception of the orthomolecular psychiatric movement. Hoffer & Osmond (1966) claim that a large proportion of individuals diagnosed as schizophrenic are likely to be vitamin B3 dependent and consider such a biochemical imbalance to be causative of the schizophrenic syndrome. The deficiency states of which Hoffer speaks will not necessarily be characterized by physical pellagrin type symptoms although similarities have been drawn between the psychological manifestations of schizophrenia and pellagrin psychosis. Thus, Hoffer (1974) postulates that schizophrenia and certain depressions are consequences of psychological niacin deficiencies. Unfortunately, therapeutic sucesses reported by the same author, following megadose administration of vitamin B3 to schizophrenics and depressives, are confounded by the concomitant application of alternative therapies. That is, in addition to vitamin B3 application, the sucessful cases were subjected to therapies including drastic dietary alteration, administration of conventional tranquilizers, antidepressants and ECT. Concurrent administration of several treatments, inhibits attribution or proportioning of efficacy to singular components such as vitamins.

A comprehensive study by Wittenborn (1975), comparing administration of 3000mg/day of nicotinic acid with a control regime of 6 mg/day to groups of 60 and 40 schizophrenics respectively for two years, has since failed to support

Hoffer's (1974) claims. In addition, the American Psychiatric Association, based on a contracted report on the assessment of megavitamin therapy (Lipton et al., 1974), have effectively dismissed claims such as Hoffer's, as being empirically and theoretically unfounded.

Dakshinamurti (1977) has noted the demonstration of abnormal EEG waking state patterns, i.e. total absence of alpha rhythms, in 10 out of 29 patients with pellagra which were normalized following 10 - 42 days treatment with niacin. Also, Goldsmith (1956,1958) reported the appearance of mental depression in human adults after 6-8 weeks of dietary induced niacin deficiencies. Finally Kety (1975) maintains that early in this century, as many as 10% of patients in mental hospitals were there owing to mental disturbances relating to pellagra.

Thus, evidence of altered psycological and electrophysiological states associated with the pellagrin syndrome indicate that niacin levels may have psychoactive relevance. Consequently, the influences of this vitamin must be considered in the psychophysiological analysis of tryptophan administration.

The second relevant aspect of niacin to the present inquiry relates to the side effects associated with megadose administration of tryptophan. A specific reaction has been ascribed to elevated niacin levels. The reaction is held to be associated with nicotinic acid not nicotinamide. Symptoms have been described as follows: flushing of the head and neck and sometimes the shoulders and arms (Finkel, 1975); warm, itchy flush an hour after ingestion (Atkins & Linde, 1977); skin turns pink, flushing itchiness and prickliness (Cheraskin et al., 1974). Cheraskin et al. (1974) maintains that neither the flushing or other side effects are dangerous. The effects are simply held to be the result of vasodilation (Finkel, 1975; Goth, 1978). This reaction was of relevance to the experimental outcome for subjects 01 and 02 (Chapter IV).

2.2.2.3 Tryptamine synthesis

As evident from Figure 2-1, tryptophan also acts as a precursor in the synthesis of brain tryptamine. The physiology of this process has been well established by Young & Gauthier (1981). In humans CSF indoleaectic acid (IAA) concentration is positively correlated with CSF tryptophan concentration. The implication from Young & Gauthier's (1981) research is that physiological variations in brain tryptophan appear significantly and positively related to tryptamine as well as serotonin turnover.

Young & Gauthier (1981) have also established the magnitude of relationship between an oral load of 3 & 6 gms of tryptophan and assumed 5HT and tryptamine synthesis measured via cisternal 5HIAA and IAA levels respectively, eight hours after administration. Both trytophan loads produced an approximate 50% increase in cisternal 5HIAA while IAA levels were doubled and quadruppled by 3 and 6gms respectively. Thus, CNS tryptamine appears more sensitive than 5HT metabolism to oral tryptophan loads. It seems that past claims of tryptamine's insignificance relative to serotonin metabolism in the manifestation of mood changes (Curzon, 1969), may be due for reconsideration in the light of Young & Gauthier's (1981) findings. The psychological significance of tryptamine elevation in relation to trytophan administration has not, as yet, been documented.

Further investigation is required in order to establish the psychobiological relevance of both nicotinic acid and tryptamine relationships to altered tryptophan metabolism. No further consideration is given to the significance of these relationships in the present thesis. Although subsequent consideration of action mechanisms is devoted to serotonin synthesis, the potential importance of alternative pathways is not dismissed.

2.3 PSYCHOPHYSIOLOGICAL AND PSYCHOPHARMACOLOGICAL RELATIONSHIPS OF TRYPTOPHAN

This section is concerned with the relationships between indices of tryptophan and serotonin metabolism and their relevance to psychological state. Such information is seen as reducing the conflict associated with relationships between tryptophan administration and mood alteration - particulalry in the therapeutic context. In addition, consideration of such relationships is considered as a necessary prerequisite to the evaluation of tryptophan's role in investigations of serotonergic functioning. Finally such information provides a background to the motivation for and evaluation of the present experiment.

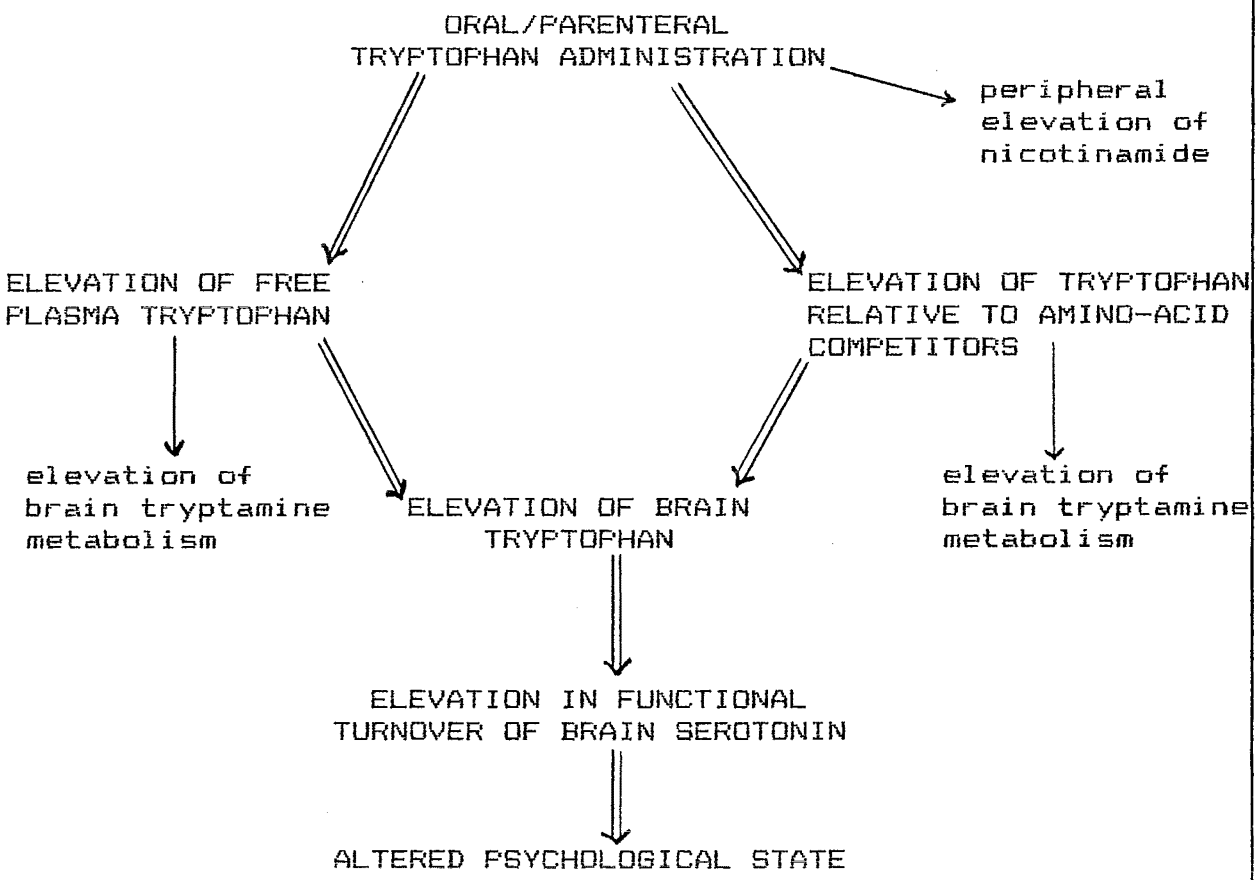
2.3.1 Plasma dynamics of tryptophan

Most investigations of the psychophysiological and psychopharmacological relationships of tryptophan in humans are limited by the inaccessibility of relevant brain metabolites. Consequently there is a need to determine whether peripheral metabolic indices can provide valid correlates of cerberal tryptophan and serotonin metabolism and of psychological state. As well as contributing to determination of action mechanisms, such parameters may provide useful predictors of psychological (particularly therapeutic) response to tryptophan administration. Two such parameters within the peripheral plasma environment, have emerged as useful indicators in the above respects.

2.3.1.1 Free and total plasma levels

McMenamy et al. (1958) demonstrated tryptophan's uniqueness amoung amino acids in its high affinity for binding to human serum albumin, predominantly at a single site, in a highly stereospecific manner. In humans, an estimated 80-90% of tryptophan is albumin bound (Pardridge, 1979). The consequence of this high 'state bound' level on availabiltiy and transport of tryptophan to the brain is uncertain. However, is commonly held that the unbound or free component is the fraction of relevance in this respect.

Figure 2-2 Summary of relationships relevant to the proposed mechanism of action for tryptophan administration



The above diagram represents a summarized overview of various psychobiological correlates of tryptophan administration in humans. The scheme represents an integration of emprically based information from past studies on tryptophan and serotonergic activity. The insertion of double arrows between processes is meant to indicate the generally accepted sequence of events for the mechanism of action appropriate to tryptophan ingestion. This hypothesis is considered the most relevant to the present thesis - particularly with respect to antidepressant action. No one study incorporates all of the above information and the majority have been limited to investigation between the proposed extremes of this chain, i.e. administration of trytophan and alteration in psychological state. The accompanying text contained in this chapter, considers the evidence relevant to relationships between the processes stated in this diagram.

(a) Diurnal variations

Tagliamonte et al. (1974) demonstrated concentrations of free serum tryptophan to be 45% higher at midnight than at noon in normal subjects. Conversely, total plasma concentrations (i.e. free + bound components) did not demonstrate significant alterations. The above findings have subsequently led to proposals of optimal times for the therapeutic administration of tryptophan. On the assumption that the free plasma trytophan fraction is of relevance to both brain concentrations of trytophan and serotonin turnover, it has been postulated that tryptophan doses will be maximally utilized to therapeutic advantage if administered at night. This was one reason for night time administration of tryptophan in the present study.

More recent investigation by Niskanen et al. (1976) has, however, failed to support the existence of marked diurnal fluctuations in free plasma tryptophan concentrations in normal subjects. These authors compared free and total plasma concentrations between healthy controls and depressed patients (both before and after antidepressant treatment). Seven measurements were made over a 24 hour cycle at 4 hourly intervals. Clearly, further investigation is required to establish the existence within and between different psychological groups with respect to circadian cycles of plasma tryptophan.

Evidence also indicates the need for consideration of dietary parameters. Young et al. (1969) demonstrated that changes in meal spacing significantly altered the diurnal pattern of plasma tryptophan concentrations. Similarly, as evident from Wurtman's (1983) demonstrations, diet composition may also account for variation in diurnal patterns and consequent relations proposed between such patterns and psychological state. Thus, there is a need to clarify the contributions of factors such as psychological status (especially depressed versus normal), dietary influences and the differences between total and free concentrations with respect to diurnal patterns of tryptophan metabolism.

(b) Seasonal variations

Coppen & Wood (1983) have considered plasma tryptophan data from drug free depressives and normal healthy controls in relation to the month of blood collection. Results indicated controls to exhibit significantly higher levels of free tryptophan than depressives in the Spring, Autumn and early Winter, while there was very little difference in the late Winter and Summer.

(c) Relationships to age, height and weight and sex

The influence of age, height and body weight on total plasma tryptophan has been investigated in normals and depressives (Banki & Molnar, 1981 (a) & (b)). No significant correlations emerged between such parameters for the combined groups. However, it was only after eliminating the effects for age, height and weight that significant differences in total plasma concentrations between depressives and normals emerged. Rose (1967) found sex differences in tryptophan metabolism which may be attributable to the changes in tryptophan metabolism associated with the menstrual cycle.

(d) Relationships to diet

A lack of dietary tryptophan has been demonstrated to cause a marked reduction in free serum tryptophan (Biggio et al., 1974), while protein malnourishment in rats leads to an increase in plasma free tryptophan (Miller et al., 1977). Coppen & Wood (1978) have demonstrated increased free plasma tryptophan values in depressed patients on high protein diet compared to those on an ordinary hospital diet.

(e) Relationships to psychological state

Total plasma differences between normals and depressives

Total plasma concentration does not generally support biochemical differentiation between groups of normals and depressives. Several studies investigating baseline differences

have indicated no difference between depressives and controls in total plasma concentration (Niskanen et al., 1976; Garfinkel et al, 1976; Riley & Shaw, 1981; Sepping et al., 1977; Coppen et al., 1973; Moller et al., 1976,1979; Whalley et al., 1980; Hoes et al., 1981). In addition, no significant differences were discernable between depressives and controls up to 6 hours following a therapeutic dose (Hoes et al., 1981; Moller et al., 1982). However, three investigations have indicated significant elevation of total plasma levels in depressives relative to controls (Garfinkel et al., 1976; Coppen, et al. 1974; Banki & Molnar, 1981 (b)). In the first case, the difference was not detected until administration of a peripheral decarboxylase inhibitor. Such evidence tentatively suggests the presence of a reduced flux of tryptophan from albumin in depression, which is masked while peripheral indoleamine synthesis is able to proceed. Finally, one investigation indicated significantly lower concentrations in depressives compared to normals (DeMyer et al., 1981).

Total plasma differences between depressives before and after recovery

Evidence emerging from comparison of total tryptophan levels in depressives before and after recovery (following a variety of antidepressant therapies), also indicates a lack of differentiation by this index (Peet et al., 1976; Coppen et al., 1973; Moller et al., 1979; Niskanen et al., 1976; Hoes et al., 1981). Although, Whalley et al. (1980) demonstrated a significant reduction following a course of ECT in severe depressives.

The value of such studies is impaired by the fact that most involved comparison of a pre recovery group with a different post recovery group. This approach overlooks the possibility that individual differences in pre recovery concentrations may relate significantly to post recovery levels. One investigation (Banki et al., 1981 (b)), indicated no difference (on mean HDS scores) between low and high total plasma tryptophan subgroups of depressives but significantly increased levels of suicidal behaviour were associated with the low plasma group. Although

high individual variability within the depressive group has been observed in more of the above studies (e.g. Whalley et al., 1980), no attempts have been made to investigate the relationship of such variability to therapeutic response - either to conventional therapies or to tryptophan.

Relevance of total plasma levels to tryptophan adminitration

The one investigation comparing therapeutic response to tryptophan, with total plasma levels in depressives, indicated no significant relationships for the group (Hoes et al., 1981). However, demand for significant group differences may have led to neglect of significant effects for select biochemical or psychological types. Until such individual evaluations are conducted relevance of this index remains uncertain.

Free plasma differences between normals and depressives

A full spectrum of conflicting relationships emerges for free plasma levels. Results range from no baseline difference between depressives and controls (Garfinkel et al., 1976; Sepping et al., 1977; Moller et al., 1976; Riley & Shaw, 1981; Whalley et al., 1980; Menna-Perper et al., 1983), to significantly lower levels in depressives (Coppen et al., 1973; Coppen & Wood, 1983) and finally to significantly higher levels in depressives (Niskanen et al., 1976). As with total levels, Garfinkel et al. (1976) demonstrated a normal-depressive differentiation following administration of carbidopa (peripheral decarboxylase inhibitor), that is, a significant increase was observed in depressives and a decrease in controls. Similarly, although no baseline differences were apparent between normals and depressives, insulin administration led to a significant decline in depresives but not controls (Menna-Perper et al., 1983).

Free plasma differences between depressives before and after recovery

Studies comparing depressives before and after recovery similarly range from no difference (Moller et al., 1979; Peet et al, 1976; Whalley et al., 1980) to significantly higher

concentrations at post recovery versus pre recovery (Coppen et al, 1973). Finally, Niskanen et al. (1976) demonstrated higher free plasma concentrations for poorly improved versus well improved depressives. Clearly such investigations are limited, as are the total plasma investigations, by the failure to take account of pre and post recovery levels at an individual level.

Total and free plasma relationships to psychological state in normal subjects

Most investigations of the relationships between psychological state and plasma tryptophan in normal individuals, have been related to single doses. In such studies monitoring of psychological state is typically limited to anywhere from two to four hours. The most frequent reports in this context are for significant concurrent elevations in total and free plasma levels and subjective ratings of drowsiness (Charney et al., 1982; Greenwood et al., 1974; 1975; Yuwiler et al., 1981). Although there are indications of similar relationships following chronic administration for two weeks (Yuwiler et al., 1981), there has been a lack of investigation of general mood altering effects following longterm tryptophan administration in normal subjects.

Value of total and free plasma concentrations as correlates of psychological state

The conflict in outcome between the above investigations contributes to the uncertainty of free or total plasma indices as reliable and valid correlates of psychological state in depressed or normal individuals. The emerging opinion that disorders of tryptophan metabolism are only of relevance in select groups of depressives (van Praag, 1981; Coppen & Wood, 1983; Foire et al., 1979; Moller et al., 1980), needs to be acknowledged. Rather than comparing large heterogeneous (psychological and biochemical) groups of depressives, focus on relationships in individuals with abnormal plasma tryptophan concentrations relative to those with normal levels may be more fruitful.

The variation in plasma tryptophan levels with respect to diet, time of day, season, sex and weight need to be considered

before relationships to psychological state can be confidently determined. It is probable that much of the conflict between the studies considered so far may relate to such differences. For example, while most investigations employed 12 hour fasting periods prior to sampling plasma, the dietary controls before this time were highly variable with respect to quantity and composition. As previously considered, dietary composition may significantly effect plasma tryptophan dynamics (Wurtman, 1982). Similarly, the failure to report tryptophan sampling times and the limitation of several studies to investigation of female subjects suggests further potential sources of conflict. Finally, while all of the above studies considered, employed similar plasma assay methods - according to Denckla & Dewey (1967) - only one (Knott & Curzon, 1972) reported data on the reliability of the procedure within their investigation. Thus, potential differences in the accuracy of measurement between studies may also contribute to conflicting outcome.

Approaches to investigation of plasma tryptophan, which take concurrent account of the above confounding influences, are demanded before the physiological and pharmacological utility of such indices can be appropriately assessed.

(g) Relationships of free and total plasma tryptophan to brain tryptophan and serotonin

If plasma tryptophan concentrations are to be considered as reliable correlates of the psychopharmacological action of the amino acid, then it is necessary to establish something of their relationship to brain tryptophan and serotonin metabolism within and across various psychological types.

Young & Gauthier (1981), maintain that total plasma tryptophan levels do provide reliable indices of brain concentration under certain circumstances and that the controversy over which is the superior index simply reflects a polarization of viewpoints. However, the same authors demonstrated the superiority of free plasma as opposed to total levels, in paralleling CSF tryptophan concentrations in humans. Other studies support existence of significant positive

correlations between free but not total plasma tryptophan and lumbar and ventricular tryptophan as well as 5HIAA levels (Curzon, 1981; Young et al., 1976). In addition, Perez-Cruet et al. (1974) demonstrated positive but non-significant correlations between free plasma tryptophan and the above CSF indices. In contrast, investigation of total plasma revealed significantly higher levels in depressed versus normal controls without concomitant changes in CSF tryptophan.

Information from rat studies also supports significant increases in free plasma tryptophan, brain tryptophan and brain 5HIAA but not total plasma tryptophan (Knott & Curzon, 1972). Similarly, concomitant decreases in the above indices (excluding total plasma tryptophan and including brain 5HT) have been demonstrated following a tryptophan free diet (Biggio et al., 1974).

The the above studies indicating a positive correlation between free plasma tryptophan and CSF tryptophan and 5HIAA do not of course prove that brain tryptophan levels and functional 5HT synthesis, in humans, is increased by tryptophan administration. However, preliminary results from psychiatric patients undergoing stereotactic surgery indicated concentrations of frontal cortex 5HT were significantly elevated following tryptophan infusion (comparable to an oral dose of 3gms) (Curzon, 1981). How this intervention related to plasma dynamics was, unfortuately, not reported. While evidence for positive correlations between free plasma tryptophan and CSF tryptophan and 5HIAA have been demonstrated in both depressed and normal controls, it can not be assumed the relationship is generalizable to all types of depression. That is, it is conceivable that certain types of depression may be associated with disorders in plasma to brain tryptophan transport, in which case such a relationship would be expected to break down.

(h) Value of plasma tryptophan concentrations

Moller et al. (1980) have reported the inability of plasma tryptophan levels to predict antidepressant response to tryptophan administration. This conclusion was however only

based on the relationship between a single plasma analysis prior to tryptophan therapy and following response to two weeks of tryptophan ingestion.

Overall, the value of plasma tryptophan levels as a valid means of selecting positive responders to tryptophan therapy remains to be determined. However, there is sufficient evidence to indicate that free plasma levels may be of relevance as indicators of brain tryptophan and serotonin metabolism and associated changes in psychological state. Evaluation of the utility of such indices still demands investigation within individuals, in order to determine the existence of relationships between psychological types and biochemical profiles. The validity of such investigations will also demand that account is taken of potentially confounding variables such as diet, time of day, season, age, sex and weight - demonstrated to relate signifcantly to plasma tryptophan concentrations.

2.3.1.2 Ratio of tryptophan to other 5 other amino acids

Several authors have argued that the plasma ratio of tryptophan to five other neutral amino acids (trp/5aa ratio) may be a more pertinent indicator than free plasma levels of changes relevant to psyhological state (Moller et al., 1976, 1980) as well as providing a more valid index of associated changes in brain tryptophan and serotonin metabolism (Fernstrom et al., 1973; Fernstrom & Wurtman, 1974; Wurtman, 1982). The blood to brain transport of tryptophan and five other neutral amino acids: tyrosine, phenylalanine, leucine, isoleucine and valine appear dependent on the same carrier molecule in humans (Pardridge, 1979; Yuwiler et al., 1977; Wurtman, 1982). Thus, it follows that access of tryptophan to the brain will depend to some extent on the balance of competition between the above amino acids.

(a) Dietary influences

Evidence from rat studies indicates the trp/5aa ratio increases following carbohydrate ingestion (Fernstrom & Wurtman, 1974). This phenomenon appears attributable to the selective action of insulin in supressing plasma concentrations of neutral

amino acids, excluding tryptophan. As Wurtman & Fernstrom (1974) have demonstrated, the action of insulin releases plasma albumin from free fatty acid bonds. Consequently, tryptophan's high albumin binding affinity results in a maintenance of plasma tryptophan levels relative to the the other neutral amino acids with low binding affinities. In contrast, protein consumption is likely to reduce the ratio, owing to the under representation of tryptophan in most protein foods relative to the other neutral amino acids.

(b) Relationship to age

Moller et al. (1980) reported a significant negative correlation between age and the trp/5aa ratio ($r=-0.53$, $p<0.001$) in a normal sample ($n=60$).

(c) Relationship to psychological state

Differences between normals and depressives

Lower trp/5aa ratios have been demonstrated in depressives relative to normals (DeMeyer et al., 1981). However, the groups compared were small, $n=18$ and $n=10$ respectively and intergroup variability was high. For this reason, more confidence is attributed to Moller et al.'s (1980) finding of no overall differentiation between depressives ($n=87$) and normals ($n=60$). There are some indications of an increase in the trp/5aa ratio with reduction of depressive symptomatology (DeMeyer, 1981). However, more pertinent findings have emerged from investigation of select depressed individuals with plasma ratios (tryptophan relative to 3 and 5 competitiors) well below the normal range. Significantly positive antidepressant response to tryptophan therapy was associated with low trp/5aa ratios, relative to depressed individuals with normal ratios - where therapeutic effect was negligible (Moller et al., 1976; 1980).

(d) Relevance to tryptophan adminstration

Firstly, findings that brain tryptophan concentration and serotonin synthesis might be dependent on the trp/5aa ratio in

humans (Fernstrom & Wurtman, 1974; James et al., 1976; Curzon, 1981) indicate that administration of tryptophan in such a way as to increase this ratio should effect increases in the above brain concentrations.

Secondly, in the psychotherapeutic context, investigations by Moller et al. (1980) have indicated the potential value of the trp/5aa ratio as a predictor of therapeutic response to tryptophan in both unipolar and bipolar depression. That is, if their total depressive sample (n=87), heterogeneous with respect the above index, was considered, then a satisfactory therapeutic response would have been of the order of 28% (comparable to the placebo effect - Wechsler et al., 1965). However, selection of patients with plasma ratios below the 30th (n=18) or 15th (n=10) percentiles demonstrated a remission frequency following tryptophan therapy of 60% and 80% respectively (i.e. of an order comparable to that following tricyclic therapy and ECT respectively - Wechsler et al., 1965). Thus, it appears the plasma trp/5aa ratio may be indicative of tryptophan metabolism disorders in some depressions, which are responsive to tryptophan therapy.

(e) Relationship of trp/5aa ratio to brain tryptophan and serotonin

A clear positive correlation has been established between brain tryptophan concentration and the trp/5aa ratio (Fernstrom & Wurtman, 1974; James et al., 1976; Wurtman, 1982) in rats. Fernstrom & Wurtman (1972, 1974) also demonstrated a positive correlation between the synthesis of serotonin and the above parameters in rats.

It was found that large increases in plasma tryptophan concentrations did not correlate with increases in brain tryptophan and serotonin (in rats) unless the trp/5aa ratio was elevated (Fernstrom & Wurtman, 1972). Similarly, Yuwiler et al. (1977) found the amino acid competition for carrier sites was quantitatively the most important factor, relative to the concentration of free and bound plasma tryptophan, in regulating tryptophan uptake to the brain.

The above findings in rats do not necessarily suggest that the tryp/5aa ratio is a more reliable indicator of brain tryptophan and serotonin metabolism in humans. However, the trp/5aa ratio has been demonstrated to more reliably reflect CSF tryptophan and 5HIAA concentrations than free or total plasma concentrations in humans (Perez-Cruet et al., 1974).

(f) Value of the trp/5aa ratio relative to plasma free tryptophan concentrations

Several comparative investigations of the two indices in both rats and humans have consistently reported the tryp/5aa ratio to be superior to free plasma concentrations as a correlate of central serotonin metabolism. (Yuwiler et al., 1977; Perez-Cruet et al., 1974; Ferstrom & Wurtman, 1972). Curzon (1981) has suggested that the variability attributed to either index may be a consequence of the plasma sampling procedures. As indicated above both indices may provide reliable correlates of brain and CSF metabolism under certain circumstances. Evidence also indicates that certain factors such as diet composition may lead to predictable changes in the accuracy of either index as a correlate of central metabolism or psychological state. Consequently, the most productive future strategies would seem best aimed at obtaining information on both parameters across a variety of psychophysiological and psychopharmacological contexts. In this way, the comparitive value of either index as a screening variable for therapeutic applications of tryptophan may be established.

Both indicies demonstrate dramatic physiological fluctuations in relation to circadian periods and dietary factors. Although, some evidence exists to support significant correlations of physiological changes in the plasma indices with brain tryptophan concentration and serotonin synthesis (Fernstrom & Wurtman, 1971; Wurtman, 1982 - in rats), it is difficult to accept that central serotonin metabolism is totally dependent on peripheral indices exhibiting almost constant and dramatic flux. Although absence of dietary tryptophan for 24 hours was demonstrated to reduce brain tryptophan by 90%, serotonin by 58% and 5HIAA by 76% (Biggio et al., 1974) in rats, the sensitivity

of the human brain in this respect remains undetermined.

Neckers et al. (1977) have indicated, that while the above plasma indices relate to brain tryptophan concentration, other central mechanisms such as changes in tryptophan hydroxylase activity in relation to brain tryptophan concentration are implicated in the regulation of brain serotonin synthesis in the rat. The potential for such regulation in human systems must be considered as a possible limitation to reliance on peripheral indicators of central effects.

2.3.2 Other potential indicators of brain tryptophan concentration

Other biochemical variables which may be of relevance to brain concentrations of tryptophan and associated changes in psychological state include the degree to which tryptophan is freed from albumin as the blood passes through the brain (Pardridge, 1979; and kinetic characteristics of the blood to brain transport system (James et al., 1976). Curzon (1969) has also proposed associations between disorders of tryptophan pyrrolase and depression. That is, it has been suggested that the activity of this enzyme is abnormally elevated in certain depressions and, thus, may reduce the amount of tryptophan normally avialable for transport to the brain. Such parameters are of relevance to the present investigation to the extent that disorders in such processes may account for psychological resistance to trytophan administration in some individuals. That is, unlike plasma tryptophan concentrations and the tryp/5aa ratio, where disorders (i.e. deficiencies) may be remediated by tryptophan loading, such therapeutic procedures would not necessarily be relevant to disorders of the transport system.

The potential for such disorders in depression has been indicated by Garkinkel (1976), where differences in tryptophan metabolism between normals and unipolar depressives were not revealed until the administration of a peripheral decarboxylase inhibitor. The increase in plasma tryptophan concentrations for depressives following this intervention, could be indicative of reduced CNS uptake of tryptophan. Similary, the findings of

Menna-Perper et al. (1983), that depressive-normal differences in free tryptophan levels were only revealed following insulin administration is indicative of potential tryptophan disorders in some depressions, other than plasma tryptophan concentration or the trp/5aa ratio.

Obviously further investigation is required to test such hypotheses. Meanwhile, the possibility of such disorders must be considered as additional sources of potential conflict in the outcome between investigations into relationships of plasma tryptophan indices, brain metabolism and psychological state.

2.3.3 Urinary indices of tryptophan metabolism

A limited number of studies have investigated the correlation of urinary catabolites, assumed to reflect tryptophan and serotonin metabolism, with psychological state. The motivation for investigation being that such products may reflect aspects of central nervous system metabolism. Other less aspiring studies are based on assumptions that such measurements may be indicative of peripheral tryptophan metabolism.

Frazer et al. (1973) demonstrated no difference in baseline urinary excretion of nine such metabolites (including kynurenine, 5HIAA and IAA) in a small group of depressed and non depressed psychiatric patients. Similarly, no changes were determined following a 2 gm oral tryptophan load. In addition, Coppen et al. (1974) found no difference in 5HIAA and IAA between severe depressives and normals or depressives before and after recovery. On the basis, of such evidence the authors claim there is no support for disorders of peripheral and central tryptophan metabolism in depression. In contrast, Garfinkel et al (1979) demonstrated significantly higher concentrations of urinary 5HIAA in depressives versus controls and significantly reduced tryptamine excretion for depressives following carbidopa administration. Such findings contributed to the conclusion of reduced CNS uptake of tryptophan in depression.

It is not considered that a great deal of importance should be placed on urinary catabolites as indicators of tryptophan

metabolism for as Klerman (1966) commented "trying to understand brain chemistry through the study of urine is like trying to find out the secret plans of the Supreme Soviet by analyzing the sewage from the Kremlin". The above investigations of urinary catabolites are also considered to suffer from many of the methodogical inadequacies directed at psychophysiological and psychopharmacological investigations of plasma tryptophan such as between group comparisons. Despite the appeal of urinary monitoring, as a less invasive biochemical procedure, relative to plasma or CSF sampling, its value as a reflector of CNS metabolism must be considered inferior. For this reason, more in depth analysis of the research on urinary catabolites was omitted from the present thesis.

2.3.4 Relevance of serotonin to the psychophysiological and psychopharmacological relationships of tryptophan

Seperate demonstrations of significant relationships between plasma tryptophan dynamics and psychological state on the one hand and between the plasma dynamics and brain tryptophan + serotonin metabolites (CSF tryptophan and 5HIAA concentrations respectively) on the other indirectly endorse the psychological relevance of serotonin with respect to tryptophan metabolism. In addition, significant positive correlations are indicated between brain tryptophan and serotonin synthesis in rats (Fernstrom & Wurtman, 1974) and in humans on the basis of CSF measurements (Young & Gauthier, 1981). Tagliamonte et al. (1971), have also indicated in studies with rats that drugs which alter serotonin synthesis (e.g. reserpine, lithium, d-amphetamine, p-chlorophenyalanine) tend to effect parallel changes in brain tryptophan concentration. Whether such drugs effect serotonin synthesis via alteration of tryptophan concentration or whether alterations in serotonin synthesis feed back to control tryptophan concentration is uncertain. However, such studies indicate close association between tryptophan concentration and brain serotonin synthesis across a wide variety of pharmacological and physiological situations.

2.3.4.1 Psychophysiological relevance of serotonin

The psychological significance of serotonin in states of depression has been indicated in physiological contexts independent of tryptophan administration. The two main sources of information in this respect come from correlations between psychological state and CSF serotonin metabolites and secondly, between postmortem brain 5HIAA concentrations and knowledge of affective state prior to death.

Measurements of CSF serotonin metabolites such as 5HIAA have been made in relation to psychological state on the assumption that such concentrations reflect brain serotonin metabolism. Several investigations have demonstrated significantly reduced CSF 5HIAA concentrations in depressed versus normal individuals (Coppen et al., 1972; Asberg & Traskman, 1981; Bridges et al., 1976; Garelis, 1981; van Praag & Korf, 1970).

Despite the apparent unanimity of results in this area, caution is required in assuming that CSF 5HIAA concentrations are reflective of brain serotonin metabolism. Young & Gauthier (1981) have demonstrated the potential distortions of measurment arising from lumbar punctures which have not been preceeded by cisternal displacement (i.e. O_2 displacement of CSF from the lateral ventricles to the lumbar sac where it is sampled). Lumbar, as opposed to cisternal fluids, appear to reflect certain biases due to the dynamics of the transport systems between the two locations. For example, 5HIAA and IAA are transported out of the spinal subarachnoid space by the same system, thus competition from the more abundant 5HIAA is likely to obscure brain relationships when the lumbar sample is not preceeded by cisternal displacement.

Other methodological problems such as the failure to match controls and depressives for age, sex and body weight - all of which may significantly effect CSF measurements (Asberg & Traskman, 1981; Banki & Molnar, 1981 (a) & (b)), reduce reliability in the use of this index. In addition, such investigations typically involve small, psychologically heterogeneous samples. Finally numerous criticisms have been

leveled at the inaccuracy and unreliability of fluorometric assay methods and probenecid techniques (Gabay, 1981). Garelis (1981) showed that probenecid administration may result in altered serotonin metabolism and psychological state. In addition, its application may lead to the unusual event of serotonin exchange between the blood and the CSF.

While the value of CSF 5HIAA as an indicator of tryptophan metabolism remains uncertain, the fact that plasma free tryptophan levels (Young & Gauthier, 1981; Curzon, 1981; Young et al, 1976) and the tryp/5aa ratio (Fernstrom & Wurtman, 1972; 1974; James et al., 1976; Wurtman, 1982) correlate positively with CSF 5HIAA, indicate that such parameters may be of more practical value as predictors of therapeutic response to tryptophan. Plasma is more acessible to biochemical analysis than CSF. In addition, the tryp/5aa ratio has been shown to be a useful predictor of therapeutic response to tryptophan (Moller et al., 1976; 1980). Finally, there is no compelling evidence to indicate the superiority of CSF 5HIAA over the plasma tryptophan dynamics as indicators of central serotonin metabolism.

In the context of postmortem investigations, Coppen (1969) reported significantly reduced hindbrain serotonin concentrations in the autopsied brains of depressed suicide victims compared to controls who died of other causes. The same author also reported significantly reduced 5HIAA in suicides versus non-suicides, with a 25% lower level in depressed versus non-depressed subjects. Such findings indicate that serotonin synthesis in the brain stem of depressives may be decreased. In general agreement were the findings of Banki et al. (1981 (b)), where symptoms relating to suicidal behaviour (as well as anxiety and insomnia) were significantly more severe in the lower third of a depressive inpatient group with respect to CSF-5HIAA concentration, relative to the highest third.

2.3.4.2 Pharmacological relevance of serotonin

Pharmacologically based inferences concerning the psychological importance of serotonin metabolism have largely been drawn from the action of certain antidepressant drugs on

this neurotransmitter's activity. Actions of certain tricyclic antidepressants in blocking serotonin reuptake, e.g. imipramine (Corrodi & Fuxe, 1968), clomipramine (Meek & Werdinius, 1970) and nortryptiline (McGeer et al., 1978) have been demonstrated. Similarly, various MAOI antidepressants have been shown to potentiate serotonergic action (Asberg & Traskman, 1981). As is evident from Figure 2-2, inhibition of MAOI will inhibit the degradation of serotonin to 5HIAA, thus effectively leading to an elevation in brain serotonin concentration. The the MAOI's and tricyclic uptake blockers can both be assumed, on the basis of indirect evidence, to increase the concentration of brain serotonin. In addition, administration of psychological depressants such as reserpine have been demonstrated to deplete both central and peripheral serotonin concentrations (Goth, 1978; Goodman & Gilman, 1980). Chronic administration of this drug has been associated with depression and suicide in humans (Goth, 1978).

Determination of serotonergic function through investigation of drug effects such as the above is hindered by their lack of specificity for serotonin. For example reserpine also leads to depletion of the catecholamines (Goth, 1978; Mendels & Frazer, 1974). Similarly, administration of many of the tricyclics mentioned above appears to be associated with a blockage of catecholamine reuptake (Duquesne & Reeves, 1982). Thus, alteration of serotonin metabolism is not the exclusive effect of the above agents. Consequently, the utility of such pharmacological evidence is limited to suggestions of the general psychological relevance of serotonin to depression. That is, there is a general indication that the both tricyclic and MAOI's act, via different mechanisms, towards a common effect of enhancing the availability of brain serotonin (Aghajanian & Wang, 1978). The above pharmacological findings are insufficient to definitively implicate altered serotonin metabolism in the pathogenesis of depression. However, in combination with the psychophysiological evidence considered previously, there is general support for theories of central serotonin depletion in some depressions. Further investigation is required to determine if serotonin depletion is paralleled by reductions in free plasma tryptophan concentrations and/or trp/5aa ratios.

The difficulties in elucidating relationships between serotonergic function and psychological state from investigation of drugs such as those mentioned in this section, with non specific/exclusive serotonergic effects, indicates a potential investigatory role for tryptophan. This proposal is forwarded and justified in the final chapter of this thesis.

2.3.5 Value of psychophysiological and psychopharmacological investigations of tryptophan

Overall, it is considered that the majority of evidence lends support to the proposed action mechanism (Figure 2-2). Most of the relevant links in the chain have been considered separately in the above discussion. Clearly, the inaccessibility of brain metabolites in humans has hindered concurrent investigation of the total action mechanism. Thus, verfication of the sequences between plasma indices and brain relationships such as tryptophan and serotonin concentrations has largely been limited to rats. That is, the sequential process of: tryptophan administration -> increase in plasma tryptophan or competing amino acids -> increase in brain tryptophan -> increase in serotonin concentration has been clearly established within rats (Fernstrom & Wurtman, 1974).

One aspect of the proposed action mechanism in Figure 2-2 which has not been sufficiently verified is whether tryptophan administration leads to a functional turnover of brain serotonin - a logical requirement if tryptophan administration is to effect an alteration in psychological state. The findings that brain tryptophan concentration correlates with serotonin synthesis does not imply a functional metabolic connection such as alteration in transmission of nerve impluses across the synapse. Similarly, correlations between plasma parameters (exhibiting correlations with brain tryptophan concentration and serotonin synthesis) and psychological state do not implicate altered serotonergic activity as mediating the relationship.

In humans the situation is further confounded by uncertainty over the relationship of CSF components such as 5HIAA to functional brain serotonin metabolism. As Grahame-Smith (1973)

has demonstrated with rats, the assumption of CSF reflection in this respect may be unfounded in the context of tryptophan administration. That is, administration of tryptophan alone, was shown to effect only slight increases in brain 5HT, more dramatic 5HIAA production and little behavioural change. In contrast, administration of tryptophan following pretreatment with an MAOI was associated with similar 5HT elevation, reduced 5HIAA relative to the former situation, and marked elevation in hyperactive behavior. The potential implication of such demonstrations is that 5HIAA monitoring, particularly following tryptophan loading, may in part be reflective of intraneuronal 5HT metabolism - that is serotonin which never becomes functionally active. Thus, it must be considered that brain 5HT turnover to 5HIAA (as measured in the CSF) in humans may not be exclusively reflective of functional serotonergic neuronal activity.

Finally, while most links in the mechanism proposed in Figure 2-2 correlate closely in time, the final aspect of altered psychological state is considerably delayed in certain contexts. That is, although some psychological correlates have been reported between 1/2 and hour to two hours following tryptophan administration in normal subjects (Yuwiler et al., 1981; Greenwood et al., 1974; 1975; Charney et al., 1982), significant antidepressant effects are generally not apparent until two weeks of administration. Thus, the rapid increase in serotonin turnover following tryptophan administration does not correlate immediately with antidepressant effects. However, such delays in psychological effect are also typical of most antidepressant drugs, including those assumed to primarily alter serotonin metabolism. For example, despite the extremely rapid pharmacological effect of such drugs e.g. MAO inhibitors can double the concentration of brain serotonin in less than an hour (Goth, 1978), antidepressant effects are generally not exerted for two weeks (Duquesne & Reeves, 1982). Thus, while elevation of brain serotonin appears requisite to the psychological correlates of tryptophan and the MAOI's it seems that more long term consequences of this process are of specific significance to antidepressant effects in both cases.

CHAPTER III

DESIGN AND ANALYSIS

3.1 INTRODUCTION

The distinguishing features of the present design include its longitudinal time base and a focus on within subject assessment and analysis. The design included extended non-treatment (baseline), placebo and active treatment phases as conditions for comparison within subjects. The single case approach led to a flexibility in design which would not have been possible in a conventional group comparative experiment. That is, experimental variables such as phase order, phase length, and dose level could be tailored to individual requirements without jeopardizing analytical and evaluative procedures. Similarly, the purpose of inquiry i.e. to investigate the mood altering properties of tryptophan, was sufficiently flexible to avoid the requirement for a homogeneous psychological sample. While tryptophan seems to have most relevance as an antidepressant there are valid reasons, to be considered in this Chapter, for investigating relationships in non depressed individuals.

Section 3.2 of this chapter provides the background and justification for the general design features of the present experiment. The following section (3.3) presents a more detailed description of experimental procedures and discusses reasons behind decisions relating to dose level, phase length and other dependent variables. Section 3.4 involves discussion of the principles guiding selection of psychological scales. A detailed description of each scale is provided along with information on the validity and reliability of the instruments. Methods used in application and processing of scales are also discussed. In the final section (3.5) data analytic procedures are presented.

3.2 GENERAL DESIGN FEATURES

3.2.1 Longitudinal time base

A decision on the longitudinal time profile was necessitated by the inclusion of comparative conditions within subjects. Recommendations relating to the required length for a fair evaluation of active treatment effects were also influential in this decision.

If tryptophan is to be classed as an antidepressant then 28 days is usually required as the minimum fair test of such qualities (Cooper,1979). Wittenborn (1978) advocates two to four weeks as sufficient for detection of anxiolytic effects and three to four weeks for the discernment of antidepressant drug effects. In a review of the therapeutic applications of tryptophan, van Praag (1981) reports that beneficial effects, if any, appear after two to three weeks with gradually increasing prominence in the next three to five weeks. The above evidence indicates a requirement for a minimum of two weeks to detect therapeutic effects. Although only some subjects were classed as depressed in the present study, 18 out of a total of 20 participants consumed tryptophan for at least two weeks.

The longitudinal time base, with daily assessment, was considered to provide a more representative sample of psychological functioning than evaluations based on single pre and post intervention measurements. That is, the former approach views psychological functioning as a dynamic process whereby meaningful changes can be assessed against the background noise e.g. circadian fluctuations. In contrast, evaluation based on single assessments or short time bases may result in unrepresentative impressions of psychological state.

3.2.2 Single case research

The decision to focus inquiry and evaluation within subjects was based on empirical demonstration of significant inter-individual differences in variables affecting the psychodynamics of tryptophan ingestion and psychotropic drugs in general. In

the context of antidepressant applications of tryptophan certain aspects of psychological and biochemical individuality have emerged as significant correlates with efficacy. As mentioned in Chapter II, factors such as the plasma trp/5aa ratio (Moller et al, 1980) and the polarity of depression (Murphy et al, 1974; Farkas et al, 1976) correlate significantly with therapeutic outcome. Chouinard et al (1978), also demonstrated the requirement for higher therapeutic dose levels in bipolar depressives compared to unipolars. Thus, it is apparent that certain individual variations mark a source for the reduction of conflict surrounding mood altering properties of tryptophan administration and indicate the probable limitation of tryptophan's effectiveness to select psychological or biochemical types. Consequently, within subject evaluation was considered more appropriate to the detection of discriminating factors than intergroup comparisons.

Evidence emerging from orthomolecular approaches to psychiatry (Hoffer, 1974) has indicated 1000 fold differences between individuals in nutrient doses required to obtain and maintain optimal biochemical and psychological states. The magnitude of interindividual variation in human pharmacokinetics is also supported by evidence from more conventional therapeutic contexts. Duquesne & Reeves (1982) report that dose requirements for the tricyclics range from 20 to 300 mg/day between individuals. High interindividual differences in drug metabolism (e.g. plasma half life and steady state plasma levels) for antidepressants: desmethylimipramine and nortripyline have also been documented Sjoqvist (1973). Such findings indicate a need to analyse individuals separately in order to remain alert to further discriminating factors.

Kratochwill (1978) notes that acknowledgement of individual differences in experimental and physiological psychology motivated the development of methodology characterizing group comparative approaches to experimentation. The group methodology, however, appears to have been motivated by the search for universal laws which could not be justifiably drawn from single cases. That is, the 'acknowledgement' here seemed not concerned with the detection and focus on individual

differences but with striving to smooth over such variability by attending to group averages. Dunlap's (1932) comment that "there is no average rat" reflects apt criticism of such early approaches to group experimentation. Similarly, in the present study, group averages were not considered relevant to acknowledgement of tryptophan's efficacy within individuals.

Although the present design structure employed single case methodology various experimental decisions were still dependent on group derived principles e.g. dose levels, administration time and the chosen composition of psychological scales. It is considered that a more ideal methodology would have involved exploration of these variables together with biochemical indicies relating to plasma tryptophan dynamics, metabolism and kinetics of the transport system within individuals. Time limits precluded execution of such ideals in the present study. However, the overall ideal of investigating and evaluating relationships within individuals was maintained. The philosophy of the present design can be considered in keeping with Allport's (1962) claim that the science of psychology should attend to the uniqueness of the individual.

3.3 EXPERIMENTAL PROCEDURE

3.3.1 Subject selection

Subjects were selected through notices posted at several locations throughout Christchurch: Canterbury University, city and surburban Health Food Stores and Christchurch Clinical School.

The employment of single case methodology allowed greater inter subject variability than would have been the case with more conventional group designs. This led to exploration of a wider range of subject and treatment variables. In contrast, group comparative approaches demand randomized subject selection and homogeneity for some experimental variables across subjects. Exclusion criteria in the present experiment were limited to the medical and psychological conditions listed on the demographic questionnaire (Appendix A).

Recipients of antidepressants, tranquilizers and analgesics were not excluded, except on grounds of medical advice. Consequently, one participant continued to consume his usual prescribed antidepressants and tranquilizers throughout the experimental period. Other subjects periodically consumed various non-prescribed painkillers over the trial period. Medical advice would have been sought regarding inclusion of 'severely depressed' (Zung, 1972) subjects. However, this situation did not arise.

All respondents met with the author for a detailed outline of the practical experimental requirements and were presented with a written outline of the general aims of the research, without compromising single blind conditions. After completing the demographic questionaire (Appendix A) subjects were given a few days to decide on participation. Subjects were in no way pressured or coerced into participation. In addition to the general undesirability of this recruitment procedure, it was considered more likely to obtain motivated and conscientious subjects under conditions of voluntary and informed consent. A profile of the final sample (n=20) appears in Chapter IV.

3.3.2 Experimental Design

At the point of entry to the program subjects were presented with the following design options:

baseline 1	tablets	washout	tablets	baseline 2
14 days	14-28 days	7 days	7-28 days	7 days

Subjects were not informed of the differentiation between or within a tablet taking phase. For 19 subjects the first tablet phase consisted of tryptophan and the second placebo, while the order was reversed for the 20th subject. The final individual designs indicate slight departures from the above pattern for 11 out of 20 subjects. This variability was due to preference on the subject's part for an alteration in design prior to or during participation, which was acceptable with respect to the design limits. In other cases subjects dropped out unexpectedly or were advised by the author to reduce the

length of participation. The design relevant to each participant is presented in Chapter IV.

It is acknowledged that it would have been desirable to place half the subjects on a placebo followed by tryptophan schedule. That is, certain significant effects have been reported in relation to the order of active treatment and placebo phases (Koch et al., 1983). The reasons against this optimization in the present investigation were as follows. For subjects seeking primarily therapeutic benefit it seemed more desirable to start them on tryptophan as soon as possible in order to determine its effectiveness. If the compound proved ineffective and/or psychological state deteriorated, subjects could be more rapidly referred to alternative therapy sources. Secondly, for all subjects, it was considered desirable to detect unfavourable reactions to tryptophan early in the program so that subjects could drop out near the start. This happened for one subject who experienced nausea on two separate occasions after consuming 6gms and 3gms respectively for three days. This individual was not included in the final analysis due to insufficiency of data. Placebo data collected prior to tryptophan intake, in this subject, would have been wasted. Finally, attempts to evaluate phase order would have required between group comparison of small numbers of unmatched subjects. With the present design, subjects who left the trial earlier than planned had completed at least part tryptophan condition.

3.3.3 Experimental tasks

During the initial meeting with the author, subjects completed the demographic questionaire, Trait and State Anxiety scales, Zung Depression scale and the HSCL. Samples of all scales appear in Appendix A, while descriptions and details on application and processing are presented in section 3.5 of this chapter. Subjects committed to proceed were given sufficient scales to cover the 2 week baseline phase. Meetings between subjects and the author were arranged at weekly/fortnightly intervals throughout the experiment to return and replenish scales, discuss progress and implement design modifications if required. Subjects were also urged to make contact with the

author more frequently, if necessary, regarding problems or queries with the procedure.

All subjects were instructed to complete a series of 16 visual analogue moodscales each morning on rising and each evening (see Appendix for samples of the scales) for the duration of their experimental program. These scales are discussed in section 3.5. Subjects were given an option regarding completion time for the evening scale but were engendered to keep as close as possible to the chosen time from day to day. Consistency was checked in this respect for each subject. Most subjects (n=18) completed the evening scale just prior to retiring while the remaining two chose an earlier period i.e. on return home from work. In addition, subjects were instructed to complete the State Anxiety, Zung and HSCL scales every seven days throughout the program, after the morning moodscale.

Instructions for scale completion were given (particularly the duration of time to be covered by each scale) and correct responding in this respect checked with each subject at the initiation of the program. Further details relating to the administration of each scale are presented in section 3.5. The above format for scale completion was uniform across the baseline and washout phases for each subject. During tryptophan and placebo phases, the only alteration to the above format was ingestion of tablets prior to completion of the evening scale. Thus, the first moodscale record for tryptophan and placebo phases represents a morning rating approximately 8-12 hours following the first ingested dose.

3.3.4 Dose levels and administration

Most recommendations for dose level are oriented towards depressed individuals. The single case approach allowed for flexibility in this parameter, in that dose levels could be adjusted on the basis of motivation for entering the study and factors such as 'how many tablets subjects considered they could comfortably swallow'. Thus, if a subject was prepared to participate on the basis of a lower than recommended dose, they could still be usefully included in the study. Before any

decisions were made regarding maximum dose levels the literature was examined for guidelines and relationships between dose level and negative/harmful side effects.

3.3.4.1 Side effects and toxicity of tryptophan

Tryptophan was considered a 'drug' within the present study due to the fact that it was administered at up to twelve times the normal daily dietary requirement. Some investigators avoid this classification of tryptophan on the basis of its status as a naturally ocurring, essential dietary component. This may account for the paucity of investigations relevant to toxicity or side effects. Comment on the inadequacy of information in this regard appears in The Side Effects of Drugs Annual: "Despite the plausibility and appeal of tryptophan to treat depression, the scientific evidence is currently inadequate to endorse either its safety or efficacy" (Blackwell, 1980).

The literature on side effects was considered in conjunction with reports on optimal dose levels before upper levels were established. Attention was given to studies investigating effects in normal (non-psychiatric) as well as depressed individuals. A limitation of most studies investigating toxicity is their short term duration, i.e. generally such studies have depended on monitoring of a single oral load or seven days administration.

Young & Sourkes (1977) have presented a list of potentially adverse reactions which relate to the increase of peripheral catabolites following tryptophan ingestion, e.g., inhibition of glucogenesis. However, there is no evidence to indicate the degree of severity of such states or of the doses and length of administration required to achieve them. With respect to the inhibition of glucogenesis, Milne (1968) has reported evidence of hyperglycemia followed by hypoglycemia after lethal doses in rats, although this was not considered a significant determinant in the causes of mortality. Other studies have reported depressed blood sugar levels in response to tryptophan administration. Domino & Krause (1974) reported that several subjects exhibited symptoms resembling hypoglycemia following a

single 3 gm dose.

Extrapolating from rats, lethal dose levels (LD50) in humans are estimated at aprroximately 6.5 mmoles/kg body weight (Gullino, 1956) or 93 gms for a 70 kg body weight. The same author also reports that acute intravenous doses of 7.5 gms have been administered to adults with no evidence of permenant harmful effects. Empirically based reports of side effects which appear with most frequency in the literature, across normal and depressed samples, include:

(1) Drowsiness (Charney et al., 1982; Greenwood et al., 1974; 1975; Hartmann, 1977, 1981; Shopsin, 1978; Smith & Prockop, 1962; Yuwiler et al., 1981). The doses for these reports range from 1-6 gms/day and length of administration from 1-49 days. In general reports were noted to occur 1/2 - 1 hour following administration and to last one to four hours.

(2) Nausea - generally mild (Broadhurst, 1970; Yuwiler, et al. 1981; Carroll et al., 1970; Charney et al., 1982; Chouinard et al., 1978; Shopsin, 1978; Wyatt et al. 1970; Brezinova et al., 1972). The nausea was typically characterized as mild and transient i.e. not resulting in vomitting and receeding 30 - 60 minutes following onset for dose ranges of 3.5 -7.5 gms/day and trial times of 14-49 days.

A limited number of investigations have been conducted into the physiological side effects of large tryptophan loads. Broadhurst (1970) following 36 laboratory investigations (n=115, dose = 6gms/day, time = 28 days), reported no evidence of toxicity in this respect. Within the same dose and time parameters, Herrington et al. (1974,1976) reported that haematological analyses: serum electrolytes, plasma protein and liver function tests, were all within the normal range.

3.3.4.2 Side effect monitoring in the present study

It was considered necessary to include some monitoring of the commonly reported side effects from the tryptophan literature and the more common symptoms (Green, 1964) that would normally be reviewed for all psychoactive drugs. Such states were monitered throughout all experimental phases. Collection of side effect information was achieved with a daily (evening) checklist (Appendix A). Formulation of this list is described in section 3.5. Its value as a reliable and valid indicator of the side effects associated with chronic tryptophan administration is uncertain but it seemed necessary to incorporate some check on side the effects reported in the literature which were not specifically covered in the standard daily scales. Measures of potentially harmful physiological/biochemical processes, were not feasible within the present study.

3.3.4.3 Optimum therapeutic dose levels

Chouinard et al. (1978) indicated the probable existence of a "therapeutic window effect" with respect to plasma tryptophan concentration. These authors demonstrated that the efficacy of a tryptophan+nicotinamide combination in treatment of severe depression diminished following a dose increase from 4gms+1gm/day to 6gms+1.5g/day, respectively. Other studies have supported the therapeutic window proposition. Herrington et al (1974, 1976) demonstrated an increase of tryptophan dose from 6 to 8 gms/day was associated with declines in efficacy. Thus, Chouinard et al. (1979) proposed an optimal dose of 6gms/day or below for unipolar depression (and above 6gms/day for bipolar depression). Other investigations, e.g., Coppen et al. (1972) did not support the above findings. A dose of 9gms/day was of significant benefit in unipolar depressives. However, the dose was split into three daily administrations compared to a single dose in the previous studies. Finally, Young & Sourkes (1977) investigated the mean daily doses involved in trials reporting antidepressant tryptophan action versus those studies reporting no therapeutic efficacy. The sucessful trials were found to use a significantly ($p<.05$) lower dose i.e., 6.1 +/- 0.6g (6 studies) compared to ineffective trials with doses of 8.7 +/- 0.9g (7 studies).

Time constraints limited the investigation of optimal dose levels within individuals in the present study. Thus, the above recommendations were considered in setting the upper dose limit for all subjects at 6gms/day. This level could also be considered well within limits established to be free of permenant harmful/toxic effects (Milne, 1968).

3.3.4.4 Peripheral pathway inhibitors

Due to the potential for kynurenine pathway induction to detract from brain tryptophan availability (following tryptophan loads), investigations have centred on the physiological effects of concomitant administration of tryptophan pyrrolase inhibitors i.e. nicotinic derivatives (Chouinard et al., 1978, 1979) and allopurinol (Shopsin, 1978). Both compounds, via different methods, can inhibit tryptophan pyrrolase - an essential enzyme for catabolism via the kynurenine course. It is assumed that inhibiting the activity of tryptophan's major catabolic pathway may increase the quota of tryptophan available to the brain.

Many studies employing this strategy have failed to make comparisons with tryptophan administration alone. Green et al. (1980,(b)) noted absence of significant alteration in total/free plasma tryptophan following a single 50mg/kg tryptophan load in subjects pretreated for 7 days with allupurinol/nicotinamide compared with subjects with no pretreatment. There is no evidence to support psychological benefits from such procedures or effects on brain 5HT turnover in humans. Thus, there is a need to establish whether (when tryptophan is administered with pyrrolase inhibitors) reduced dose recommendations (Young et al., 1981) are effective. Peripheral pathway inhibitors were not available in the present investigation.

3.3.4.5 Pyridoxine supplements

Pyridoxine (vitamin B_6) supplements have also been administrered with tryptophan. The rationale here is that increased kynurenine catabolism may overload enzymes dependent on the co-enzyme pyridoxal phosphate, unless pyridoxine is given to increase its availability. It is assumed that this procedure may

help prevent over-accumulation of tryptophan metabolites such as kynurenine (Young et al., 1981).

Green & Aronson (1980) demonstrated that pretreatment with pyridoxine+tryptophan was associated with a plasma kynurenine concentration (following a single load) half that of subjects where pretreatment consisted of tryptophan alone. Thus, if increased plasma kynurenine concentrations following chronic tryptophan administration are responsible for diminished transport of tryptophan to the brain, then concomitant administration of a pyridoxine supplement may be instrumental in promoting CNS concentrations of tryptophan. Coppen (1976) did not, however, find any difference in antidepressant efficacy when tryptophan was given with or without pyridoxine. It was not feesible to include pyridoxine suppliments in the present thesis.

3.3.4.6 Administration

In all cases tryptophan and placebo were administered as a single oral, daily dose. Both subtances were in the form of 500 mg tablets and of identical shape and weight. There was a slight coat colour difference between tryptophan and placebo which was not noticed by subjects. Description of tryptophan and placebo composition appears Appendix C. Daily doses were packaged and dated in opaque brown envelopes and subjects were instructed to open each days packet immediately prior to ingestion so that comparison between different days tablets was avoided.

Findings that plasma free tryptophan levels were 45% higher at midnight than at noon (Tagliamonte et al., 1974), and that brain serotonin turnover reflects changes associated with this tryptophan quota (Bartlett et al., 1981; Curzon, 1981; Fernstrom & Wurtman, 1972; Gessa et al., 1972; Tagliamonte et al., 1971,1974), suggests tryptophan may have maximal psychological effect if ingested at night. Kynurenine pathway activity has also been demonstrated to be relatively inactive at this time (Curzon, 1969), thus, tryptophan may be less utilized by this competing (non therapeutic) pathway if taken at night.

The decision to have subjects consume tryptophan in the

evening was in part motivated by the above findings. Evening tryptophan consumption also served as a precaution in cases of subjects experiencing drowsiness following ingestion. It was assumed that such an effect could be turned to advantage if tryptophan was consumed prior to retiring. Related support for a single nightly dose comes from investigations of the therapeutic effects of antidepressants. Recent psychiatric findings support the preference for a single nightly dose regime due to improved compliance and the benefit of hypnotic effects (Lehman, 1978).

3.3.5 Placebo administration

The incorporation of a placebo phase in addition to active treatment and non treatment periods (baseline) was seen as a desirable control for the components of drug administration which are independent of the drug composition. Past studies have indicated dramatic effects following placebo administration which resemble the effects of active drugs in many respects. For example, Lemann (1978) notes a case of severe addiction to placebo where the "patient took 25 pills a day and required systematic withdrawl". Similarly, Green (1964) reported the manifestation of such adverse conditions as vomiting, sweating, diarrhoea, constipation and skin rashes following placebo administration. Positive correlations between increased placebo dose and the above effects were also demonstrated. Frank (1961) reported significant improvement in conditions such as ulcers, headaches, warts and numerous psychiatric conditions following administration of pharmacologically inert substances.

These kind of demonstrations indicate the need for comparison of tryptophan consumption with a placebo in order that relationships of psychological state to the biochemical activity of tryptophan may be separated from other administrative processes. While many past investigations have endorsed tryptophan's antidepressant value at a level comparable with the tricyclics, such trials do not establish tryptophan's superiority over placebo. In respect to the latter, the literature is controversial.

One of the main ethical objections to placebo administration

in clinical trials relates to the withholding of more efficacious treatment. In some cases this has led to comparison of the experimental drug with therapeutically established compounds. For one subject (16) in the present study, who was experiencing moderate to severe levels of depression (Zung, 1972), it was considered preferable to avoid exposure to placebo. This subject was referred to the study by Student Health (Canterbury University) and was consuming the tetracyclic antidepressant mianserin on entry to the program. Thus, it was considered more desirable to compare ratings on mianserin with tryptophan, having incorporated a suitable washout period between the two phases. This subject was still informed that he might receive placebo on any night of pill consumption. Another depressed subject (02) continued to consume his formerly prescribed antidepressant medication throughout the total trial. In the case of the remaining three depressed subjects, administration of placebo, as opposed to referral to more efficacious therapies, can only be justified on the basis that all these subjects gave informed consent with respect to the possibility of receiving placebos and were not experiencing severe depression according to Zung's (1972) classification.

3.3.6 Dietary/nutritional considerations

The validity of the present investigation is limited due the lack of information on dietary patterns over the trial period which may have effected plasma tryptophan levels and psychological state. As Wurtman (1982) has indicated, adequate assessment of dietary influence would require detailed information on diet composition, meal spacing and investigation of associated biochemical changes. It was considered that such procedures would have increased the burden of experimental requirements to an unreasonable level for most subjects. Consideration of dietary influence in the present experiment was limited to information on whether or not participants were vegetarians. On the assumption that vegetarian diets may represent significant differences from omnivorous diets in protein-carbohydrate balance, it was considered this division may contribute to differences in biochemical and psychological states. Wurtman (1982), has demonstrated significant effects of

protein - carbohydrate balance on availability of plasma tryptophan for brain transport.

3.3.7 Information supplied to participants

Subjects were supplied with full information on the requirements of the experiment while at the same time protecting the methodological validity of the investigation. A brief outline of the general constitution, occurrance and utilization of tryptophan was provided. Subjects were given a restricted outline of the design which omitted to differentiate between tryptophan and placebo conditions. Subjects were then informed that they could receive tryptophan or placebo on any night of both phases. By keeping subjects blind to the presence of tryptophan and placebo phases it was hoped to deter focus from on the expectation of a substance crossover between tablet periods.

Participants were supplied with assurances regarding the safety of tryptophan. This required the provision of limited information on side effects. Subjects were not given any specific information by the author regarding the reported antidepressant and hypnotic effects of tryptophan, although some were aware of the reported effects used for advertising the product. Subjects were not blind to the general purpose of the experiment and are likely to have become more oriented to the relevance of specific states such as anxiety, depression and alertness throughout the course of the program. Subject awareness in this respect was not considered to threaten experimental validity provided subjects remained blind to the tryptophan and placebo phases. It was hoped the above presentation would aid subjects in making more responsible and informed decisions over participation. For example, it may have been unacceptable, to those seeking therapeutic effects, to be subjected to placebo administration. At the conclusion of the experiment, subjects were informed of the blind conditions. Finally, all subjects were assured of confidentiality and anonymity regarding the display of results.

Problems relating to the validity of the present design are discussed in Chapter IV.

3.4 PSYCHOLOGICAL SCALES

3.4.1 Principles guiding selection

The focus of inquiry in the present study depended to some extent on the psychological profiles of participants and their motivations for entering the experiment. For example, it was considered appropriate to investigate antidepressant effects only in depressed individuals. However, the selection of scales was necessarily made prior to establishment of the above information. The primary guiding considerations for instrument selection combined information from past studies on the psychological effects of tryptophan administration along with the aim to incorporate instruments sufficiently flexible and senitive to detect change in a potentially wide range of psychological types. With this background, preference was given to the most reliable and valid available scales as well as those that had demonstrated sensitivity to psychotropic drug effects.

The most frequent psychological and somatic states to emerge from the literature in relation to tryptophan administration can be classified as follows:

(1) Significant antidepressant effects. The following authors report antidepressant effects equivalent to commonly prescribed tricyclics such as imipramine and amitriptyline: Coppen et al., 1972; Jensen et al., 1975; Lindberg et al., 1979; Rao & Broadhurst, 1976; Herrington et al., 1974,1976; Chouinard et al., 1979; Broadhurst, 1970; Kline & Shah, 1974. The above studies were based on significant group responses as criteria of effectiveness. Numerous additional investigations report significant antidepressant responses for some participants (Farkas et al., 1976; Carroll et al., 1970; Dunner & Fieve, 1975; Moller et al., 1976; Moller et al., 1979; Moller et al., 1980; Murphy et al., 1974).

(2) States relevant to sleep parameters. Various investigators have reported reduction in sleep latency (i.e. time taken to fall asleep) (Hartman, 1976; Hartman & Spinweber, 1979; Brown et al., 1979). Hypnotic effects of tryptophan were demonstrated to be

significantly greater than placebo but inferior to conventional tranquillizers (Brezinova et al., 1972).

(3) States outside the therapeutic area which may be classed as undesirable side effects, e.g. drowsiness (Yuwiler et al., 1981; Carroll et al., 1970; Smith & Prockop, 1962; Charney et al., 1982; Shopsin, 1978; Hartman et al., 1981), nausea (Carroll et al., 1970; Broadhurst, 1970; Charney et al., 1982; Chouinard et al., 1978; Shopsin, 1978) and euphoria (Charney et al., 1982; Smith & Prockop, 1962). Other more somatic or physical states include lethargy (Yuwiler et al., 1981), blurred vision (Carroll et al., 1970), dizziness (Thomson et al., 1982) and insomnia (Prange et al., 1974).

Attention was given to scales demonstrating sensitivity to as many as possible of the above areas of psychological and physical states (excepting those relating to sleep parameters). The chosen scales had to be appropriate to a wide range of psychological profiles. One extreme of the subject range could be considered to comprise normal (non depressed) or adaptive functional states and the other extreme disturbed states relating to moderate levels of depression (Zung, 1972) or anxiety.

Another consideration guiding selection of psychological scales was the requirement for self rating instruments. Design demands such as daily mood rating (for up to 84 days), frequent measurement of anxiety and depression states combined with a mobile population (compared with hospital situations) clearly established the logistic need for self-assessment. Additonal factors such as the need for trained or experienced administrators in the case of 'other' rater instruments promoted selection of the self-rating approach. A final positive justification for employment of self rating instruments comes from a comment by Raskin et al. (1967): "ultimately it seems it is the patient's interpretation of the altered physiology of the drug state that will determine therapeutic sucess". Although it can not be assumed that self rating scales are the best means of obtaining such information, it would seem they are logically more closely connected to the process than 'other' rater instruments.

3.4.2 The chosen scales

The remainder of this section contains a sequential description, evaluation and justification for the scales employed. The details relating to administration and processing are included with each scale assessment.

3.4.2.1 Visual Analogue Mood Scale (VAMS)

(a) Description

This rating scale was first developed and applied by Norris (1971) in an assessment and comparison of the subjective effects of Nitrazepam (benzodiazepine) and sodium phenobarbitone (barbiturate). As evident from Appendix A, the instrument comprises a series of 16 (100mm) analogue scales, each scale being marked at its end points by opposing adjectives descriptive of a particular mood state. Subjects are required to rate their feelings at a given moment by marking positions relative to the extreme adjectives for each scale. For the purposes of the present discussion the instrument is referred to as the VAMS.

Visual Analogue scales have become increasingly popular in recent years (Hamilton, 1978). Such scales have been considered to overcome the difficulty of establishing the most desirable number of response grades. Visual Analogue scales allow the rater freedom from forced choice response categories. Such scales have been demonstrated to be particularly sensitive and valid indicators of drug effects in normal and psychiatric subjects (Kellner, 1971,1972; Brand, 1969; Aitken, 1969).

The motivation for construction of the VAMS related to the detection of sedative effects of drugs such as the above. Having established the scales they were grouped by Norris (1971) into four categories relevant to clinical aspects of sedation:

(1) Mental sedation or intellectual impairment (items: 1,4,11,13)
(2) Physical sedation or bodily impairments (items: 3,5,6,16)
(3) Tranquilization or calming effects (items: 2,7,8,12)
(4) Other types of feelings or attitudes (items: 9,10,14,15)

The items comprising the mental and physical sedation categories were combined to produce single composite change scores which indicated significant overall drug effects as well as discrminating between drugs (nitrazepam and phenobarbitone) and dose levels (Norris, 1971).

It was not until the work of Bond & Lader (1974) that a scale structure based on a large sample of normal subjects was established through factor analysis. These authors administered the scales to 500 normal, drug free subjects. Following principal component factor analysis, three factors with eigenvalues exceeding 1 were selected which accounted for more than 61% of the variance. As indicated from Table 3-1 the resultant item custers show some overlap with Norris's (1971) more intuitive groupings.

Herbert et al. (1976) have also conducted extensive factor analytic procedures with the above scales to determine factors in normal volunteers. In this study two principal factors emerged to account for 62% and 10% of the variance respectively. These authors claimed to have based such analyses on 735 cases, however, this number turns out to be composed of 32-45 repeated ratings for only 38 subjects. In this respect it was considered preferable to utilize Bond & Lader's factor loadings for data reduction purposes in the present investigation.

(b) Validity

The factor structure developed by Bond & Lader (1974), based on normal subjects, was considered to provide a valid means of data reduction for the VAMS in the present study. That is, most participants in the present investigation could be considered free of psychological disturbance. The alternative of establishing an independent strucure on the basis of the present sample could not be justified given that the final sample was considered to be composed of only 8 depressed individuals and 12 normals.

Table 3-1 VAMS scale groupings with associated factor loadings based on administration to 500 drug free normals

Factor	Scales	Loadings
alertness	1. alert - drowsy	0.827
	11. attentive - dreamy	0.792
	6. energetic - lethargic	0.776
	4. clear headed - muzzy	0.755
	5. well co-ordinated - clumsy	0.642
	9. quick witted - mentally slow	0.635
	3. strong - feeble	0.618
	15. interested - bored	0.614
	12. proficient - incompetent	0.593
contentedness	13. happy - sad	0.823
	14. amicable - antagonistic	0.738
	8. tranquil - troubled	0.697
	7. contented - discontented	0.677
	16. gregarious - withdrawn	0.594
calmness	2. calm - excited	0.845
	10. relaxed - tense	0.677

(from Bond & Lader, 1974)

Despite the lack of information regarding the construction of the scale, subsequent applications to the detection of psychotropic drug effects have demonstrated appropriate sensitivity. Bond & Lader (1974) demonstrated significant sensitivity, particularly for their contendedness and calmness factors, in a study comparing single doses of butobarbitone and sodium flurazepam versus placebo in normal subjects. Lader & Tyrer (1972) also demonstrated significant drug effects for propranolol and sotatol versus placebo on scales incorporated under the alertness and contentedness dimensions. Finally, Greenwood et al. (1975) applied the scales to the detection of subjective effects following acute oral tryptophan administration (5gm dose) in normal subjects. In this investigation four scales from the alertness factor indicated significant discrimination from placebo.

(c) Reliabilty

The characterisitcs of the VAMS, so far described, present difficulties in the establishment of reliability. The assumed transitory nature of the dimensions under study makes the calculation of test-retest measures of reliablity inappropriate. Investigations based on alternate forms or split half comparisons have not, to date, been conducted. However, Bond & Lader (1974) have reported relatively high correlations between similar scales, i.e.

(1) alert-drowsy and attentive-dreamy, r=0.66 (factor 1)
(2) contented-discontented and happy-sad, r=0.65 (factor 2)
(3) muzzy-clear headed and lethargic-energetic, r=0.56 (factor 1)

Such correlations were based on scales with face value similarity. The scales used for each correlation also belong to the same factor grouping according to Bond & Lader's (1974) structure.

(d) Justification for inclusion

The VAMS represents, in the author's opinion, the best compromise between the features described previously as guiding scale choice. The principal reasons for the relevance of this scale to the present inquiry are as follows:

(1) The scale comprised a concise and rapidly executed means of assessment for subjective feeling relevant to the moment of completion, making it a suitable instrument for twice daily administration to subjects.

(2) The original formulation of the scale was oriented towards the detection of psychotropic drug effects and subsequent applications have demonstrated its sensitivity in this respect.

(3) The scale has shown sensitivity to drug effects in normal subjects.

(4) At face value, many of the adjectives comprising the scales bear relevance to frequently reported effects associated with past investigations of tryptophan administration. This is particularly apparent in the case of scales comprising the dimension of alertness (Bond & Lader, 1974), such as 'drowsiness' and to a lesser extent the items relating to the contentedness dimension which could be considered relevant to 'antidepressant' effects or states of 'euphoria'.

(5) The VAMS has demonstrated sensitivity to effects associated with tryptophan administration in normal subjects (Greenwood et al., 1974; 1975) - particularly the dimension of alertness.

(6) Finally, the factor structure (based on normal subjects) determined by Bond & Lader (1974) could be considered to provide a reasonably valid method for reducing the number of mood ratings (from 16 to 3 dimensions) for most of the participants in the present study.

(e) Application and processing

The VAMS was completed twice daily by subjects for the duration of the experiment. The scales were administered according to the instructions formulated by Norris (1971) and consistent with subsequent applications of the scale.

Scales were measured and scored to the nearest 5mm. Norris (1971) and Bond & Lader (1974) both claim to have measured the scales to the nearest 1mm, however, data relating to the achievement of accuracy in this regard is not documented. In the present investigation, measurement to the nearest 1mm proved unrealistic, i.e. tests of accuracy following repeated scoring of the same ratings only proved to be acceptable at a measurements to the nearest 5mms for the present author. In addition the rating marks made by some subjects frequently extended over 1-2mm. Measurement to the nearest 5mm allowed an increase in the speed and reliability of the scoring process relative to 1mm trials. The reduction of scales to Bond & Lader's (1974) factorial dimensions, is described in section 3.5.

3.4.2.2 Zung's Self Rating Depression Scale (SDS)

(a) Description

Zung (1965) gave the following reasons for developing the scale:

"We were interested in having a scale for assessing depression in patients whose primary diagnoses were that of a depressive disorder, which would fulfil the following: it should be all inclusive with respect to symptoms of the illness, it should be short and simple, it should quantitate rather than qualitate, and it should be self administered and indicate the patients own response at the time the scale is taken."

The selection of SDS items was dependent on extensive factor analysis of concepts from several clinical sets of depressive symptoms. (Grinker et al., 1961; Overall, 1962; Friedman et al., 1963). The final item wording was based on representative patient statements relevant to each symptom. As is evident from Appendix A, the scale comprises 20 symptoms rated on a four point scale of severity. The rating categories represent an update in wording (Zung, 1974) from the original 1965 form to include extreme choices i.e. 'a little of the time' was updated to 'none or a little of the time' and 'most of the time' to 'most or all of the time'. There are also two changes to item wording to be noted i.e. no. 4: 'I have trouble sleeping' to 'I have trouble sleeping through the night' and no. 6: 'I still enjoy sex' to 'I enjoy looking at, talking to and being with attractive women (or men)'.

(b) Validity

The data base from which selection of SDS items was made was comprehensive in its incorporation of clinical concepts (factorially ordered prior to selection). The representativeness of Zung's (1965) final selection, with respect to clinically relevant concepts of depression, is less certain. Zung (1974) maintains that that symptoms exclusive to one theoretical orientation were purposely omitted in an attempt generalize the

scale's relevance across different concepts of depression.

Evidence of concurrent validity has been demonstrated by significant correlations between specific depression scales e.g. Beck Inventory: 0.76 and Hamilton Scale: 0.56 (Zung, 1969).

The pattern of normative data (Zung 1965) is supportive of the scale's discriminating power with respect to depressives, recovered depressives (observed to be free of their complaints and improved clinically), other psychiatric disorders (admitted as depressives and later discharged with other primary classifications) and normal individuals (professional staff & general medical and surgical patients).

More recently, larger samples of normative statistics have been prepared by Zung (1969,1971,1972). In all Zung's studies the means for the depressed samples were significantly ($p < .01$) higher than those of the normal groups, substantiating the power of the SDS for screening purposes and collaborating the utility of the scale in quantiatively discriminating between depressed and normal subjects. However, owing to the lack of demographic information in some of these samples Zung's data was not relied upon in the present study for judging the status of participants. Knight et al. (1983) have recently reported data for a comprehensive normal sample (N=1173) (Table 3-2). The sample appears significantly broader based in terms of occupational status than Zung's (1965,1968,1971 or 1972) control groups. Knight et al.'s (1983) sample yielded a higher mean score relative to Zung's (1965) normal group (but comparable or lower relative to Zung's (1969,1971,1972) later reports) as well as distinct age category differences and a significant relationship for sex and total SDS scores. Females were shown to score significantly higher ($F=84.73$, $p<.0001$), the difference correlating negatively with age.

Given the normal versus psychiatric bias of the present sample, most judgements regarding the depressive status of individuals were based on Knight et al.'s (1983) data. Reference was made to Zungs (1972) established categories, relating to magnitude of depression i.e.

	SDS index	approx tot. score
mild-moderate	50 - 59	40 - 47
moderate to severe	60 - 69	48 - 55
severe	70 and over	56 and over

Some reservations in using Knight et al.'s (1983) normative data relate to the assumption that such calculations were based on the 1965 form, i.e. there is no reference to Zung's later works. It is also unclear from Zung's investigations exactly when the revised form was implemented with respect to his normative data.

(c) Reliability

Zung (1974) reports a split half reliabilty estimation based on correlations of odd and even items of $\alpha = 0.73$ ($p<0.01$). This is in keeping with Knight et al.'s (1983) estimate of internal consistency ($\alpha = 0.79$). The meaningfulness of internal consistency in a scale measuring a clinically heterogeneous concept such as depression is uncertain. The use of a total (global) score, in the expectation that contributing items are internally consistent, may mask meaningful variability between item clusters composing the scale. Rickels et al. (1970) reported isolation of two major and three minor factors emerging from the factorial analysis of ratings by 700 neurotic, depressed patients. This result indicates the potential existence of separate item clusters which may be clinically meaningful in the sense of allowing a finer analysis of the symptom profile. Thus, the sensitivity of depression ratings in the present experiment may have been reduced due to dependence on total scores.

(d) Justification for inclusion

In order to justify investigation of the antidepressant action of tryptophan in the present study, it was necessary to include a means of screening and assessing participants for depressive symptomatology.

Zung's stated view of depression is as follows: "Depression swings to a pathological state" (Zung,1974). Thus, depression is

conceived of as a state quantitatively removed from normal psychological functioning. For the purposes of screening individuals for the presence or absence of 'depressive' symptomatology, qualitative versus quantitative concepts of depression seem less important. If the scale is to be utilized as an indicator of changing state over time for 'non - depressed' individuals then the impact of the above alternatives on scale construction and utilization is more pertinent. The capacity of the SDS in this respect has not been demonstrated and cannot be assumed. Zung (1967, 1968, 1971, 1972, 1973) has consistently reported significant mean differences in SDS scores between normals and depressives (i.e. quantitative). However a qualitative basis to this difference is indicated by the disparate factor structures emerging from analysis of the two samples (Zung, 1971; 1972). Consequently, the value of the SDS beyond a screening device for normal subjects in the present investigation is questionable in that SDS changes in normal subjects are likely to relate to a qualitatively distinct structure from that in depressives. Thus, changes in repeated administrations of the scale in normal subjects were treated cautiously and in conjunction with moodscale ratings (where meaningful changes for normal subjects are more established).

There is a lack of evidence indicating the sensitivity of this scale to drug effects, however it has been demonstrated to discriminate between and endorse the established antidepressant superiority of ECT over tricyclics (Cole, 1964; Klerman & Cole, 1965; Zung, 1974). Also, Rickels et al. (1970), reported significant therapeutic benefits, for amitriptyline and trimipramine over placebo, in neurotic depressed outpatients.

(e) Administration and processing

As is evident from the scale format (Appendix A), responses are rated on a four point scale which quantifies experience of the symptom. Items 1,2,4,6,8,9,10,11,17,20 are worded symptomatically positive while the remainder are worded symptomatically negative in order to avoid response bias. Thus, scoring for positive items was 1,2,3,4, and for the negative items 4,3,2,1 for the categories: none or a little of the time,

some of the time, a good part of the time, most or all of the time respectively.

The scales were administered according to the written instructions at the top of the form (from Zung, 1965; 1974). The author was present during the initial completion of the scale by each participant. No subjects raised uncertainties with respect to item comprehension and after completion verbal checks ensured subjects had responded as they intended. As noted previously, scales were completed at the initiation of the program and weekly thereafter until termination of the trial. Processing of scales was limited to presentation and comparison of total scores. The total scores and the consequent depression status according to Zung's (1974) outline and with respect to Knight et al.'s (1983) normative data are presented within each subjects profile and analysis.

Table (3-2) Normative data for the SDS from Knight et al. (1983) - all estimations based on total raw scores

Age	Male			Female		
	N	mean	SD	N	mean	SD
16-19	46	33.00	5.57	47	37.20	7.12
20-29	136	30.61	6.60	132	34.37	6.80
30-39	111	30.67	6.28	109	35.28	8.23
40-49	88	30.52	7.11	85	34.45	7.30
50-59	81	33.40	7.06	85	36.85	6.98

3.4.2.3 State-Trait Anxiety Inventory (STAI)

(a) Description

As is apparent from Appendix (A), the STAI (developed by Spielberger et al., 1970) comprises two separate, 20 item, self administered forms corresponding to theoretically distinct concepts of anxiety. Self evaluation Questionnaire (1) purports to quantify anxiety according to psychological State, while (2) is intended to measure Trait qualities. In the authors' words: "State anxiety (A-State) is conceptualized as a transitory

emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened autonomic nervous system activity. A-States may vary in intensity and fluctuate over time. Trait anxiety (A-Trait) refers to relatively stable individual differences between people in the tendency to respond to situations perceived as threatening with elevations in A-State intensity." Thus, the scales are distinguished by the time reference required for response, with the State form referring to "right now" or "at this moment", while the Trait form asks for repsonse in "general".

Selection of scale items was based on the processing of three existing measures of Trait concepts of anxiety (Cattell & Sheier, 1963; Taylor, 1953 and Welsh, 1956). Only items exceeding a correlation of .25 with any of the above scales were considered for inclusion. Original attempts at differentiating the State and Trait forms purely on the basis of the separate time references for response (i.e. item contents and question formulation being equivalent) were unsucessful. The present scales demonstrate retention of only five content equivalent items (2 with identical wording).

(b) Reliability

Test - retest correlations, reported by Spielberger et al. (1970), are reasonably high for the Trait scale when taken (for a normal group) before and after relaxation instruction, a difficult IQ test and films of fatal or serious injury accidents. Trait correlations ranged from .73 (retest=104 days post test) to achieved r=.33 for both occasions. This is to be expected, given that State measures should exhibit sensitivity and Trait measures stability with respect to stress specific changes in situation.

Alpha coefficients were uniformily high, ranging from α=.83 to α=.92 for State and α=.86 to α=.89 for Trait scales across all normative samples (freshmen, undergraduates and high-school students) (Spielberger et al., 1970). These findings are in keeping with Knight et al.'s (1983) estimates of α=.93 for State and α=.87 for Trait scales based on a normal (N=1173) sample.

Spielberger et al. (1970) have reported a reduction in the alpha coefficient for the State scale under conditions of increasing psychological stress, indicating a reduction in item homogeneity in such situations. Thus, depending on the measurement situation, attention to individual items may be more informative than sole reliance on total scores. For the purposes of the present investigation, processing and analysis of ratings was limited to total scores.

(c) Validity

Spielberger et al. (1970) have demonstrated reasonable concordance for the STAI A-Trait with (1) IPAT Anxiety Scale (Cattell & Scheier, 1963) and (2) Taylor Manifest Anxiety Scale (TAMS) (Taylor, 1953). Correlations with IPAT are around .76 while those of the TAMS are slightly higher. The same authors have cited significant correlations of Trait scores with dimensions of commonly used personality tests - also purporting to assess enduring qualities of psychological profile. For example, PRF (Jackson, 1967) dimensions of aggression, impulsivity and endurance and the EPPS (Edwards, 1954) dimension of abasement have produced significant correlations with Trait total scores.

The validity of the State scale has been convincingly demonstrated by its authors. Significant differences were reported on total scores and 19 individual items between a standard administration and a stress condition (where subjects had to imagine their feelings prior to an important final exam).

The limitation of normative samples in the manual to young students (college freshmen, undergraduates and high school students) and smaller groups of psychiatric and other medical patients was considered less pertinent to the present investigation than the sample base for Knight et al.'s (1983) presentation of norms (see Zung discussion for description of this sample). The need for age and sex specific norms has been demonstrated and met by these authors. Some reference was made to Spielberger et al.'s (1970) norms for depressive and anxious psychiatric patients and these are included in Table 3-3 along

with Knight et al.'s (1983) data.

Reports of STAI application are detailed in the mannual and in further endorse its status with respect to construct and criterion validity. However, there is a lack of documentation relating to its application in psychotropic drug trials.

(d) Justification for inclusion

The demonstrated sensitivity of the scales for measuring Trait and State anxiety in normal and patient populations were considered appropriate attributes for the present experimental requirements. Lack of information regarding measurement sensitivity to psychotropic drug effects is obviated by otherwise comprehensive demonstrations of discriminating power across various stress situations.

Inclusion of the Trait scale at the start of the experiment was considered to provide a useful indicator of relatively stable psychological characteristics, which were subsequently considered in relation to other more dynamic experimental variables. Indications of the concordance between the Trait scale and personality tests outlined above, as well as the demonstrated stability of Trait scores across altered states, is relevant to the present study in view of evidence for "drug - personality" interactions (McNair et al., 1970).

Finally, given the clinical blur surrounding partitioning of anxiety and depressive disorders (McNair & Fisher, 1978), it seemed appropriate to incorporate measures of both concepts in order that this communality could be explored. The meaning of significant correlations, 0.54 between SDS and State scales and 0.70 between SDS and Trait scales in a normal sample (Knight et al, 1983) is uncertain but the possibility that "in the general population, low levels of anxiety and depression also tend to covary consistently" is suggested by Knight et al. (1983).

(e) Administration and processing

Instructions for administration of the STAI were executed according to directions in the manual (Spielberger et al., 1970) with Trait completion preceeding that of State. The author was present during the completion of the Trait and initial State scales. It was verbally established that all subjects were aware of the 'time reference' distinction between forms. Subjects raised no uncertainties regarding item semantics or response demands when questioned.

Table (3-3) Means and SD's for A-State and A-Trait scales (from Knight et al., 1983) and for depressed and anxious psychiatric patients (from Spielberger et al., 1970)

	Male			Female		
Age *	n	mean	SD	n	mean	SD
A-State scale						
20-29	134	29.69	6.34	133	34.11	7.64
30-39	110	29.92	7.41	110	34.47	10.18
40-49	84	29.31	7.71	86	32.47	7.57
50-59	74	30.32	7.71	83	32.11	8.40
depressive	28	54.43	13.02			
anxious	60	49.02	11.62			
A-Trait scale						
20-29	137	32.68	7.37	135	36.85	8.41
30-39	112	32.96	8.18	111	38.39	10.18
40-49	87	32.13	7.92	86	36.61	8.36
50-59	80	34.40	8.57	88	36.70	8.86
depressive	28	53.43	12.90			
anxious	60	48.08	10.65			

* only age categories relevant to the present investigation were included

As is apparent from the scale forms (Appendix A), half the State items i.e. 1,2,5,8,10,11,15,16,19 and 20 were worded symptomatically negative and the remainder positive. In the case of the Trait scale only items 1,6,7,10,13,16 and 19 are symptomatically negative with the remaining 13 positive.

Response categories: 'not at all','somewhat','moderately so' and 'very much so' were scored 1,2,3,4 respectively for positive items and 4,3,2,1 for negative items. No scales contained missing data for any subject. Analysis was confined to discussion of total scores within each subject and State-Trait correlations across subjects, as mentioned above.

3.4.2.4 Hopkins Symptom Checklist (HSCL)

(a) Description

The HSCL is a self report symptom inventory comprising 58 items (see Appendix A) rated on a four point scale of distress, which are, according to Derogatis et al. (1974), "representative of the symptom configurations commonly observed amoung outpatients." Various altered forms of the scale developed both prior to and following the establishment of the HSCL are available. Development of all available forms can be traced to an extended format, the 'Discomfort Scale' established by Parloff et al. (1954) and designed for use as an improvement measure in studies of psychotherapy. The HSCL-58 is still considered preferable in terms of sensitivity and reliability over the shorter form by Derogatis et al. (1974).

A series of factor analytic procedures have consistently isolated five principal dimensions (Table 3-6). This structure was demonstrated to exhibit a high level of invariance, for both psychiatrists and patients ratings, in a sample of 1066 anxious, neurotic outpatients (Derogatis et al., 1971). Independent investigations by Mattsson et al. (1969) and Williams et al. (1968), employing self ratings from 404 and 1115 anxious, neurotic outpatients respectively, also yielded five principal factors. The first four factors in both studies were highly coincident in item composition. The fifth factor considered by Williams et al. (1968) as a more general depression dimension was similar in structure to a combination of Mattsson et al.'s (1968) 'anxious depression' and 'somatic depression' factors. The results of these two investigations are supportive of Derogatis et al.'s (1971) more recent structure in terms of the commonality

of the items composing the essential five dimension division of the above studies.

The orientation of this scale towards 'symptom manifestations' of anxiety and depression is justifiable with respect to its utilization in therapeutic drug trials. That is, Lipman et al. (1968) found the SCL (an extended form of the HSCL) to provide a more sensitive indicator of therapeutic change than 'non symptom' focused criteria of change - such as global improvement scales. The major focus of utilization has been in psychiatric outpatients presenting with anxiety and depressive conditions. Normative data is available for such groups as well as a 735 normal (non psychiatric) sample on the 5 principal factors (Table 3-4).

(b) Reliability

Reliability estimates for the HSCL-50 appear in Table 3-5. Internal consistency estimates (α coefficients) i.e. the average of item correlations within each dimension, are uniformily high. Test-retest coefficents were based on measurements taken a week apart for a sample of anxious, neurotic outpatients (N=425). Once again a high level of stability is demonstrated in this respect. Values for inter-rater reliability indicate there may be reasonable agreement between self concepts of the dimensions under study and clinical definitions/criteria of the same.

(c) Factorial Invariance

Derogatis et al. (1974) have also provided information relating to the factorial invariance of the HSCL-58 symptom dimensions. This property is concerned with the generalizability of dimensions to contexts (i.e. populations, experimental circumstances etc.) beyond that on which the structure was determined. Concern with this property is of particular relevance to the present inquiry, given that the final sample was composed mostly of individuals who could not be considered as "anxious neurotic outpatients".

Consistency measurments in this respect (Derogatis et al.,

1971, 1972) have been limited to variables such as social status, diagnostic classification (i.e. psychopathological) and to patients versus psychiatrists ratings. Given the small N (20) and the heterogeneity of the present sample it was not considered justifiable to conduct an independent determination of factor structure in this study.

Despite concern over relevance of the factorial structure to the present sample, there is evidence indicating the sensitivity of the proposed dimensions in normal (non psychiatric) samples. The structure has been demonstrated to differentiate clinically based judgements of normal versus neurotic patients (Rickels et al., 1972).

Table 3-4 Mean factor scores and SDs for the HSCL symptom dimensions from three normative samples

Factor	anxious neurotics		depressed neurotics		normals (Oakland sample)	
	mean	SD	mean	SD	mean	SD
somatization...	1.91	.59	1.89	.53	1.15	.27
obsessive compulsive.....	1.95	.67	2.30	.68	1.16	.27
interpersonal sensitivity....	2.00	.68	2.33	.67	1.12	.24
depression.....	2.04	.63	2.62	.63	1.14	.28
anxiety.....	2.22	.67	2.45	.68	1.13	.26

(from Derogatis et al., 1974)

(d) Validity

Concern with the criterion validity of this scale has centered around its major applications to date i.e. detection of the effects of psychotropic drugs. Clinically relevant findings have been obtained by the HSCL for therapeutic effects of anxiolytic drugs (Rickels et al., 1971; Uhlenhuth et al., 1966, Hesbacher et al., 1970), withdrawl from major tranquilizers (Covi et al., 1973) and antidepressant effects of tricyclics (Raskin et al, 1970). The HSCL has also been demonstrated to differentiate significantly between imipramine, diazepam (tranquilizer) and placebo in depressed outpatients (Covi et al., 1973).

With respect to construct validity, Derogatis et al. (1970) reported high agreement between clinical (psychiatrists) and empirical (structure determined by factor analysis) definitions of the five HSCL dimensions.

(d) Justification for inclusion

One of the principal reasons for including the HSCL in the present study related to the significant representation of somatic symptomatology relative to the Zung and state anxiety scales. As well as the factorial dimension of somatization there is a reasonable representation of somatic items in the depression and anxiety dimensions. Kiev (1974) claims the reported/ documented incidence of depression (in the U.S.) is likely to be much higher due to "nonrecognition..." often resulting "...from somatic symptoms which mask the depressed mood or serve to explain it".

Other researchers view such symptoms as significant identifiers of depressive states. In this respect several categories of relevant symptoms can be identified:

(1) Sleep disturbances e.g. insomnia, early morning waking, frequent waking and various alterations in the qualitative and quantitative dynamics of the REM and short wave cycles have been extensively documented by Feighner (1974). Snyder (1969) reports general consistency between the degree of sleep disturbance and

the apparent degree of depression.

(2) Gastrointestinal disturbance. Chaplan (1974) cites the gut as being the most commonly attributed "target organ" for somatic expression of depressive disorders. Consideration has been given to associated symptoms or functional disturbances e.g. abdominal pain, nausea, vomiting and diarrhoea.

(3) General fatigue or reports of loss of energy, listlessnss, languor, tiredness have been frequently associated with depressive disorders Karno & Hoffman (1974).

(4) Pain: notable relationships have emerged between specific pain experiences e.g. headaches, backaches, abdominal pain and apparent depression (Sternbach, 1974; Cassidy et al., 1957).

The etiological significance of such symptoms in depression is uncertain, however their implication by association with such disorders indicates that monitoring of somatic symptoms may aid in the identification of depressive states.

Another reason for including the scale relates to its demonstrated sensitivity in psychotropic drug trials - including antidepressants, and separate demonstrations of its sensitivity to detect emotional change in normal (non-psychiatric) individuals. The factor structure demonstrated by Derogatis et al (1971) and utilized in the present study distinguishes dimensions of depression and anxiety which provide useful adjuncts to measurement of the same states by the Zung and State scales. The reduction of HSCL data to factor scores is described in section 3.5.

Table 3-5 Reliability estimates for the HSCL symptom dimensions

factor	internal consistency reliability (coefficient α)	test-retest reliability	interrater reliability (intraclass r)
somatization	.87	.82	.73
obsessive-compulsive	.87	.84	.77
interpersonal sensitivity	.85	.80	.80
depression	.86	.81	.64
anxiety	.84	.75	.67

Table 3-6 Definitions & contributing items of the HSCL symptom dimensions

symptom dimension	contributing items	dimension definition
somatization	1,4,12,14,27, 42,48,49,52, 53,56,58	...reflect distress arising from perceptions of bodily dysfunction. Complaints focused on cardiovascular gastrointestinal, respiratory and other systems with marked autonomic medication are included. Headaches, pain and discomfort localized in the gross musculature and other somatic equivalents of anxiety...
obsessive-compulsive	9,10,28,38, 45,46,51,55	...symptoms that are closely identified with the clinical syndrome of this name. ...focuses on thoughts, impulses and actions ...experienced as unremitting and irresistable by the individual, but are of...an unwanted nature. Behaviours indicative of a more general cognitive difficulty also...

Table 3-6 continued:

symptom dimension	contributing items	dimension definition
interpersonal sensitivity	6,11,24,34,36, 37,41	...focus on feelings of personal inadequacy and inferiority, particularly in comparison to other persons Self deprecation, feelings of uneasiness and marked discomfort are characteristic...as are acute self-consciousness and negative expectancies regarding interpersonal communications.
depression	5,15,19,20,22, 26,29,30,31, 32,54	...reflect a broad range of the concomitants of a clinical depressive syndrome. Symptoms of disphoric mood and affect are represented as signs of withdrawl of life interest, lack of motivation and loss of vital energy. Feelings of hopelessness and futility as well as other cognitve & somatic correlates...
anxiety	2,17,23,33,39, 50,57	...associated clinically with high manifest anxiety. General indicators such as restlessness, nervousness and tension are represented as are additional somatic signs e.g. "trembling". Items touching on free-floating anxiety and panic attacks are also included.

(from Derogatis et al., 1974)

3.4.2.5 Side effect checklist

The checklist of negative side effects (Appendix A) appeared on the back of the evening VAMS. Subjects were asked to check and mark the appropriate category only if they had experienced any of the symptoms during that day. There was also a category for unspecified symptoms. The motivation for including this list stemmed from reports of negative effects associated with

tryptophan administration in past studies, the most commonly listed side effects of tricyclic antidepressants (Feighner, 1974) and finally the most common negative, somatic symptoms associated depressive disorders (Kiev, 1974). Repetition of conditions/symptoms already included in the formal scales was avoided. For example, 'drowsiness' is one of the most commonly reported negative effects associated with tryptophan administration, however, this dimension was represented in the VAMS.

No defense is presented in respect of the statistical validity or reliability of the scale and consequently the information obtained from this source was not subjected to any extensive evaluative or statistical processing. Justification for its inclusion was based on the need to monitor negative effects relevant to tryptophan administration which were not available in a concise established scale suitable for daily administration. The incidence of effects reported in this context was noted in relation to changes emerging within and across phases from the other data sources. This information is reported in assocation with each subject's analysis (Chapter IV).

3.4.2.6 Additional daily questions

As is evident from the morning and evening VAMS scales, several additional questions were inserted at the top of these response sheets by the author. The insertion of date and identification information was principally to facilitate orderly processing of scales. Responses to time of completion allowed checks of consisitency in this regard for all participants. The question on menstruation allowed investigation of this event in relation to changes emerging from the other scales and was particularly noted for females indicating experience of premenstrual tension. Responses to the question on drug consumption were also related to changes emerging from the alternative data sources. Subjects were instructed that this question included alcohol consumption. Finally, inclusion of the question relating to unusual or traumatic changes was considered necessary in the case of such events relating to sudden changes in VAMS ratings.

3.5 ANALYSIS

3.5.1 Time series data

Time series data may simply be defined as a data series with time as an independent variable. Such an approach to data collection, as employed in the present investigation, has obvious advantages over ostensibly time independent approaches in psychological inquiry. That is, organismic processes relevant to the discipline (behavioural, emotional, biochemical) represent dynamic patterns. However, the approach does not represent the rule as Gregson (1983) notes, "The most common methods of representing quantitative results in psychology are frozen outside time; thus they deliberately average out much of the sequential structure that holds any sparse clues to the nature of processes within the organism." Thus, ignorance of time as a variable may suggest ignorance of the process being studied i.e. a dynamic process comes to be viewed statically.

The evaluation of time series data does, however, present difficulties unique to this mode of investigation. A historical and current debate reigns over the merits of two major approaches to evaluation, namely: visual or statistical analysis. Kazdin (1982) maintains, in the context of the social sciences, "In single case research, statistical tests are occasionally used to evaluate the data, although this practice remains the exception rather than the rule." Visual evaluation involves the visual inspection of graphed data and subsequent formulation of a judgement regarding the consistency of data points over time. Kazdin (1982) states "When the data meet the criteria for visual inspection ... there is little need to corroborate the results with statistical tests." However, the literature turns out to be conspicuously lacking in the explication of guidelines for visual evaluation. The gap is frequently filled by statements to the effect that, because evaluation is restricted to time series exhibiting 'dramatic' intervention effects there is no need to investigate the principles or rules underlying such judgements. However, there are reasons, to be outlined below, that even when faced with dramatic effects, visual judgements may be biased. Strict adherance to exclusive acknowledgement of 'dramatic'

effects seems short-sighted - particularly in the context of exploratory investigations. That is, attention paid to less dramatic (but statistically significant) effects may lead to methodological refinements which later estabish their relevance.

It is the present author's opinion that the methods incorporated by visual evaluation provide valuable and necessary aids in the design and analysis of time series processes. One major advantage would seem that it allows the investigator close contact with the unprocessed data set in a rapidly interpretable form. Data presented in this manner provides a valuable initial indication of the outcome, including all aspects of the raw variability which may otherwise have been lost through statistical techniques such as averaging.

Parsonson & Baer (1978) state "Persons confronted with graphed operant data usually have access to the primary data ... They can perform their own data analysis and reach their own conclusions, because the details necessary to do so often have not been obscured, coalesced or dissolved via mediation by a computer or statistical tables". However, while the lack of methodological documentation inhibits replication of statistical analysis, it should not deter investigators from employing such methods. In fact, for the purposes of replication, visual analysis must also present the procedures followed for making judgements based on visually presented data - it is not enough to simply present the graphed results.

3.5.1.1 Autocorrelation

The statistical analysis of time series data in single case research has historically involved adoption of techniques originally designed for between group evaluation e.g. t and F tests and repeated measures anova. An assumption of such procedures - that of independence between the stochastic component of data points - turns out to be frequently violated by time series data sets. Jones et al. (1977) demonstrated the violation of this assumption in 83% (total=24) of time series data sets i.e. significant correlations between the error component of sucessive data points were demonstrated. This

ubiquitous phenomenon is termed 'serial dependency' or 'autocorrelation'. Demonstration of the phenomenon simply indicates that the data does not exhibit a random process over time, which explains its frequent occurance in time series data, i.e. as Jones et al. (1977) state "The reason that one should expect serial dependency is that people and their environments do not behave or function randomly over time". Because the phenomenon is limited to the error component of data points the distortions arising from the application of such tests to serially dependent data will exclude deterministic parameters such as the mean. Rather, the correlation of error components threatens estimations of significance, leading to a conservative bias in the presence of negative autocorrelation and a liberal bias (the more common occurence) in the presence of positive autocorrelation (Hartmann et al., 1980; Padia, 1973; Scheffe, 1959). Thus, the application of traditional inter-group tests of significance can not be justified without demonstrating the absence of a significant level of serial dependency. The presence of serial dependency has also been demonstrated to corrupt the reliability and accuracy of visually based judgements (Jones et al., 1977), although it is unclear whether the bias parallels that for statisical evaluation.

3.5.1.2 Time series analysis

The threat of serial dependency on the evaluation of time series data has contributed to the development of analytical methods to test for and remove the potential bias it confers. The statistical methodology developed for this purpose is simply referred to as Time Series Analysis. Where the focus of evaluation is to determine the influence of intervention effects, as in the present study, the approcach is termed interrupted time series analysis (ITSA)(Gottman & Glass, 1978; Hartmann et al., 1980).

While accomodating any effects associated with serial dependency, ITSA determines whether there is a significantly reliable change in level and trend from one phase to the next. In short, the goals of ITSA are to model the structure of the stochastic component of the time series data. Once a fitting

model is determined the systematic part of the error can be subtracted from each observation leaving the residuals free of serial dependency. With the assumption of independence between data points assured, conventional t tests can then be applied to assess the characteristics of changes over time and with respect to intervention effects. One restriction on the employment of ITSA concerns the recommended number of data points per phase. Kazdin (1982) notes estimates range from 20 to 100. The prominent founders and practitioners of ITSA e.g. Box & Jenkins (1970) recommend 100, Gottman & Glass (1978) at least 50 and Padia (1973) at least 50.

Evidence from the above authors suggests the differencing errors resulting from data sets of less than 50 points may critically effect the ITSA outcome. That is, "Under-differencing leaves serial dependency in the series and over-differencing introduces unwanted serial dependency" (Hartmann et al., 1980). According to Jones et al. (1977), the final effect of too small an N will be to conservatively bias tests of statistical significance. This results from the misidentification of the degrees of differencing required to bring the series to stationarity.

It is the present authors opinion that time series analysis offers a valuable supplement to visual analysis, provided the required assumptions such as a sufficient number of data points are met. As well as detecting and dealing with the hazard of serial dependency, the methodology allows separate analysis of changes relating to level and trend. In the case of the present investigation, it was considered the shortage of data points per phase would provide a major threat to the validity of ITSA procedures. For this reason the procedure was declined in favour of visual and statistical procedures described below.

3.5.2 Analytical procedures

3.5.2.1 Visual Analogue Moodscales

(a) Processing

The information obtained from the 16 scales was condensed to three dimensions following application of the relevant processes from Bond & Lader's (1974) factor analysis. The program written for this purpose appears in Appendix B. The procedure was as follows: scales 1,2,3,5,7,11,13 and 15 were reversed in order that the scores towards the 100 scale pole were consistently representative of positive attributes and those towards the 0 pole representative of the negative attribute. The next steps achieved by the factor extraction program (Appendix B) were to multiply each dimension score by its associated factor loading (Table 3-1), then sum the composite scores within each factor and divide the total by the summed loadings. The program itemizes the different processes followed in the case of missing data, e.g. in the case of a missing dimension score, the factor score was calculated on the remaining dimensions relevant to that factor.

(b) Visual analysis

Once in the condensed form, the first step towards analysis involved graphic representation of the three factors across all phases for each subject. As mentioned previously, the criteria for formulating what proponents claim to be valid, visually based judgements from graphed presentations of time sereis data have rarely been explicated. As Parsonson & Baer (1978) simply note, "determination of change is dependent on the change being of sufficient magnitude to be apparent to the eye". On the basis of comments in the literature (e.g. Baer, 1977; Jones et al., 1977; Parsonson & Baer, 1978; Kazdin, 1982) the consensus appears to be that one should only pay attention to dramatic changes. For the purposes of the present investigation attention was focused on dramatic alterations in those characteristics considered most pertinent by Kazdin (1982) to adequate visual inspection. These characteristics are typically statistically based concepts e.g.

changes in mean, level, trend and latency of change. The procedure followed in the present study was to state the most obvious visual indicators for each subject, to establish the potential bias from autocorrelation and finally to determine the agreement with statistical outcome. Graphed data was also considered in conjunction with the additional daily questions, side effect reports and weekly scale scores.

(c) Statistical analysis

Autocorrelation tests

Autocorrelation coefficients were computed within baseline, tryptophan and placebo phases, for most subjects, on the three mood factors (both morning and evening series). Coefficients were also computed on the combined series (consecutively combined morning and evening data) for subject 01. Combined series calculations for remaining subjects were omitted, as there was no graphical representation of this data and it was assumed that sufficient information could be obtained from the separate morning and evening series. There is some contention in the time series literature over the merits of estimating autocorrelations separately (within) as opposed to across pre and post intervention phases. Glass et al. (1975) and Kazdin (1982) advocate the former procedure on the assumption that interventions may affect the relation of data points to each other.

In order that autocorrelation reflects the stochastic component of the error process, data points of the time series must be separated by equal intervals (Hartmann et al., 1980; Jones et al., 1977), i.e. as Hartmann et al (1980) note "...irregular or variable intervals are likely to disguise or alter the pattern of autocorrelations that would otherwise be obtained." Data in the present study was considered to meet this requirement, in that scale completion time rarely varied outside two hours from day to day. Autocorrelations are generally computed for lags of N/4, where N is the number of data points of the series to be tested (Box & Jenkins, 1970; Gottman & Glass, 1978; Hartmann et al., 1980). With larger lags computations

become increasingly unstable due to the dependence on fewer observations.

The results of autocorrelation estimates for N/4 lags are presented for the relevant phases within each individual following the graphed results. Significant presence of this feature was acknowledged as a caution against placing too greater weight on graphical analysis and led to omission of statistical evaluation in some cases. The formula and and subsequent program written to test for the presence of autocorrelation appears in Appendix B.

(d) T Tests

T test calculations were performed in order to compare adjacent phase means. In general, calculations were limited to comparisons between baseline, placebo and tryptophan phases. Significant results were only taken seriously where the relevant phases were free of significant levels of autocorrelation. Results from such calculations are presented within each subject (Chapter IV). In many cases t test calculations were based on different N's between phases. In cases where there was a significant difference between the sample variances a more conservative estimation of the t statistic and associated degrees of freedom was employed as advised by Nie et al. (1975).

(d) C statistic

Finally, the C statistic, promoted as a quantitative method for the detection of trends in time series data (Tryon, 1982), was applied to this purpose. Justification for application of this statistic rests on the premise that its operation is independent of the stationarity (i.e. heterogeneity / stability of the mean, variance and autocorrelation) of the series. Tryon (1982) maintains the procedure can be sucessfully applied to series with as few as eight points per phase - this was indicated by Young's (1941) paper outlining the original formulation of the statistic. He demonstrated the unreliability of the approximation to the type II curve with samples of $n<8$, while for $n<8-50$ the approximation curve was acceptable with little

increase in $\beta 2$ values for n=8 through to 50.

The formula for the C statistic is as follows:

$$C = 1 - \frac{\sum_{i=1}^{N-1} (Xi - Xi+1)}{2 \sum_{i=1}^{N} (Xi - X)^2}$$

That is,

$$C = \frac{1 - \text{Sum((N-1)consecutive diffs associated with the series))}}{2 \times \text{Sum squared deviations from their mean}}$$

(numerator: independent of trends)

(denominator: indicates trends)

Therefore, C evaluates how large squared deviations from the mean are (i.e. reflects trends) relative to the sum of the squared consecutive differences (i.e. independent of trends). The Z statistic (achieved via division of C by its standard error (Sc)) is then checked for the determination of significance.

That is, $Z = \frac{C}{Sc}$ where $Sc = \frac{N-2}{(N-1)(N+1)}$

The standard error is entirely a function of sample size, thus, as with other statistical procedures, a significant Z can always be found for any value of C given a sufficiently large N.

Although presented as a "simplified time series analysis" by Tryon (1982), the methodology does not claim to parallel the conventional complex methods of Box & Jenkins (1976). The two approaches are similar to the extent that they represent

statistical methods for analysing temporally ordered data series to determine if interventions have produced reliable changes in the scoring pattern. However, the C statistic attempts to accomplish less than conventional time series analysis, a major limitation being its inability to separate the changes in level from changes in slope. Thus, as Tryon (1985) has more recently stated the C statistic is "an omnibus test regarding whether or not any non random trends exist".

In the present study, the C statistic is seen to serve as a more objective adjunct to visual analysis. In this manner, the confluence of the two approaches may increase confidence in the process of data interpretation. The major justification for its application over Box & Jenkins (1976) methods is the requirement for as few as eight data points per phase (Young, 1941). Although clearly less powerful than Box & Jenkins (1976) approach, the methodology appears to present a relatively simple and parsimonious procedure for detecting the presence of trends in time series data.

Application of the C statistic

Initially the statstic is applied to the baseline series. It is preferable that the baseline data is free of significant trends as this allows for a more powerful subsequent application of the statistic. Secondly, the statistic is applied to the appended baseline and first treatment phase: significance here indicating that the treatment period departs from baseline.

If significant trends exist in the baseline data, two less powerful subsequent applications are available, both involving the establishment of a comparison series composed of difference scores between the baseline and treatment phases. The more powerful alternative involves fitting of a regression line to the baseline data. The comparison series is then obtained by subtracting trend line values associated with the first baseline point from the first treatment point, then the second from the second until exhaustion,

i.e. comparison series = baseline(x) - treatment(x) (x=1,n)

where n is the length of baseline or treatment phase.

The second, simpler and less powerful approach involves a comparison series obtained by subtracting consecutive baseline points directly from treatment points. The comparison series produced by either of these methods is then tested by the C statistic, with significance indicating that the treatment phase departs from the baseline trend.

In the present investigation, morning and evening series were tested separately (except in the case of subject 01, where the combined series was also tested). In most cases, the C statistic was applied to the baseline-1 phases within subjects (n=14 days). Secondly (in the absence of baseline trends) the tryptophan phase (where n>8 days) was appended to the baseline-1 and the C statistic applied again to test departure from baseline-1. The shortness of the washout and baseline-2 phases precluded comparison with placebo period (except for subject 01). However, the main object of inquiry concerned whether tryptophan phases demonstrated a significant departure from baseline. Visual analysis and t tests (where appropriate) facilitated comparison of placebo with baseline-1 and trytophan phases.

In cases where the baseline-1 series contained significant trends, the comparison series was constructed via the less powerful method of subtracting consecutive baseline points from consecutive tryptophan points. The preferred procedure of fitting a regression line to the initial series was abandoned due to violation of the assumptions for this procedure. That is, regression analysis requires that "the sample is drawn at random" and "that each array of Y for a given combination of X's follows the normal distribution" (Kim & Kohout, 1975). Such conditions were not characteristic of the present data series.

3.5.2.2 Weekly scales

Total weekly scores for the SDS, State Anxiety and HSCL scales are presented within each subject's analysis (Chapter IV). Results in this context were considered in relation to noticeable changes within or between phases for each subject and in relation to VAMS ratings. Data from the weekly administration of the HSCL was processed according to the factorial structure established by

Derogatis et al. (1974) (Table 3-6). Factor loadings for the individual items were obtained from Derogatis et al. (1971). Items were multiplied by their loadings. Then, the composite scores relevant to each dimension were added and divided by the associated sum of the factor loadings. The factor scores from this process are presented for each subject in the result section. The program written to achieve calculation of factor scores appears in Appendix B. Zung, Trait and State anxiety scores aided in determination of subjects' anxiety and depressive status.

3.5.2.3 Clinical versus experimental/statistical significance

There is a need to address the issue of whether statistically significant results have psychological meaning in the present study. It is probable that statistically based inferences will result in Type I errors if clinical criteria of change are invoked. That is, the direction of separation most frequently cited is for a statistically significiant finding having trivial clinical relevance. This dichotomy may widen in cases of large N (N=data points in the present study), due to the dependence of statistical significance on sample size. Thus, if N is sufficiently large, entirely trivial effects will be found to be statistically significant.

The departure of statistical evaluation from clinical relevance has been employed as an argument against engaging statistical methodology in clinical trials (Baer, 1977). However, statistical analysis may be of value in detecting trends that would otherwise be passed over on the basis of stricter clinical criteria of change. Thus, statistically based judgements should not necessarily be dimissed as irrelevant if they fail to match the more conservative clinical criteria for success or failure.

In the present study, employment of statistical methodology was seen as a means of introducing some degree of objectivity to the evaluation process. In addition, small statistical effects may indicate the chance of greater effects under replication or design reconstruction in future research. Statistical evaluation

also presents some safeguard against experimenter bias. Kratochwill (1978) found that significantly more studies employing statistical analysis reported low improvement rates relative to non statistical investigations. Thus, while the discrepency is usually in the direction of more conservative clinical than statistical interpretation of change, there is a danger that in the absence of statistical validation the experimenter may tend towards positively biased clinical conclusions. It is of course possible that a real clinically meaningful improvement may remain statistically undetected. These factors are further considered in relation to the present results (Chapter IV & V).

It is the authors opinion that in drug evaluation studies such as the present one statistical criteria of change should be considered in conjunction with clinical criteria. However, in the present investigation, where professional and experienced clinical opinion was not available, evaluation depended on the variety of analytical procedures outlined above. In the final analysis, opinion was volunteered by the author regarding the psychological significance of experimental results.

CHAPTER IV

RESULTS AND EXPERIMENTAL DISCUSSION

4.1 INTRODUCTION

The first section of this chapter (4.2) presents evaluation and conclusions relating to results within subjects. Section 4.3 presents a description of the sample and evaluation of results across subjects. Finally, in section 4.4 factors relevant to the validity and generality of results are discussed.

4.2 WITHIN SUBJECT PROFILES AND ANALYSIS

This section contains consecutive presentations of subject descriptions, experimental procedures and results from visual and statistical analysis for each participant. Each presentation is followed by brief evaluations and conclusions focused on relationships between tryptophan administration and psychological state. Result presentation exhibits considerable variability between subjects owing to the diversity in psychological status and differences in experimental variables such as dose level and phase length. However, there are some consistent aspects of presentation across subjects.

Each analysis begins with a brief subject description, including assigned psychological status. Psychological status was formulated with reference to normative data provided by Knight et al. (1983) on the SDS and STAI scales and Zung's (1972) depression categories based on SDS scores. Specific features such as premenstrual tension and vegetarianism were only included if subjects responded positively. Following a description of experimental variables, results are presented for weekly scales, daily mood ratings, total sleep time, side effect quality and severity and any extra information relating to effects such as premenstrual tension or reports of unusual happenings.

Assessment of depression and anxiety status depended on intial ratings, except when subsequent ratings exhibited

stability, in which case this information contributed to assessments. For all subjects, visual and statistical analysis of daily mood ratings focused on comparison between baseline 1, tryptophan and placebo phases where sufficient data were available. Breaks in the graphed mood factors indicate missing data. In some cases absence of or insufficient ratings during the placebo phase limited comparison to baseline and tryptophan periods. Autocorrelation estimates were limited to the phases ammenable to visual and statistical analysis. C statistic applications were confined to baseline and tryptophan phases for most subjects due to the inappropriateness of comparing non adjacent phases e.g. tryptophan versus placebo. Statistical comparison of side effects and hours of sleep between baseline 1, tryptophan and placebo phases was presented where data were available. Reports of unusual happpenings and drug consumption were considered in relation to altered mood ratings.

In cases where female subjects responded positively to suffering from premenstral tension, consideration was given to changes in mood ratings, side effect reports and weekly scales during the premenstrual phase. The phase of the menstrual cycle associated with premenstrual tension varies considerably among both researchers in this field and those claiming to experience the syndrome. That is, some authorities consider the relevant phase to be confined to one to seven days prior to menstruation (Wilson & Rennie, 1976) while others consider up to 14 days prior to the onset of bleeding is more usual (Brush, 1979). A period of 14 days prior to menstrual onset is taken as the premenstrual phase in the present study. The purpose of this consideration was to determine whether psychological changes relating to the experimental conditions might have been confounded by factors coincident with the premenstrual phase.

4.2.1 Subject 01

(1) Demographic variables

age(yrs): 39 sex: female height(cms):173
weight(kgs):50.80
(below desirable weight range

drug consumption: regular consumption of: vit. A,B,C and E
vegetarian: yes
tryptophan experience: - consumed prior to this project in the context of a dietary supplement
motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

Low initial and subsequent SDS scores (with respect to Knight et al.'s (1983) norms), together with a 'general interest' motivation for participation was seen as confirmatory of a 'non depressed' status.

(b) Anxiety status

With respect to Knight et al.'s (1983) norms, this subject exhibited a low score indicating freedom from significant levels of anxiety symptoms.

(3) Experimental variables

(a) Dose level(gms/day): 6

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	28days	7days	28days	7days

(c) Extra details

Scale completion time was regular with missing data limited to the first baseline HSCL rating. Participation continued uninterupted for the 84 day program with no tablets (trytophan/placebo) being forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-1-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan				wash		placebo			bs2
day	01	07	14	21	28	35	42	49	56	63	70	77	84
scale													
zung	24	24	26	24	26	22	31	33	30	25	28	31	28
state	25	22	22	24	26	26	23	43	40	22	26	31	23
HSCL	-	74	67	66	68	63	68	79	72	62	67	75	91

Table 4-1-2 HSCL factor scores

	baseline 1			tryptophan				wash		placebo			bs2
day	01	07	14	21	28	35	42	49	56	63	70	77	84
factor													
1	1.18	1.18	1.08	1.08	1.19	1.08	1.08	1.26	1.16	1.08	1.08	1.45	1.98
2	2.07	2.07	1.67	1.64	1.64	1.54	1.89	1.77	2.03	1.41	1.73	1.89	1.89
3	1.12	1.12	1.00	1.00	1.00	1.00	1.00	1.34	1.00	1.00	1.00	1.00	1.18
4	1.18	1.18	1.09	1.00	1.09	1.08	1.09	1.27	1.16	1.00	1.09	1.16	1.44
5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.75	1.15	1.00	1.00	1.13	1.47

Comment on weekly scale scores

This subject was characterized by consistently low scores on the above scales. There was a noticeable increase in the State scores for the two weeks following the cessation of tryptophan and a similar increase of less magnitude in the HSCL scores. However, this change could not be meaningfully related to other variables. The baseline 2 (bs2) peak for the final HSCL (total) rating could be related to reported flu experience at this time.

Reference to the factor score distribution for the HSCL also demonstrates considerable consistency throughout the entire series, except for the rise in baseline 2 ratings, which was predominantly attributable to factor 1 i.e. somatization - a dimension in keeping with the flu characteristics reported. HSCL factor scores were close to the means reported for a normal sample (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

There was a lack of variation across all phases for both morning and evening series in this case. Similarly, there was an absence of noticeable change in level or slope between phases. The only marked changes in the morning series (Figure 4-1-1) concerned the concurrent troughs for all 3 mood factors in the washout and baseline 2 phases and the slightly separated but more exaggerated troughs in factors 2 and 3 of the baseline 1 phase. The washout dips on day 5 of this phase, coincided with reports of no sleep on the previous night. On days four and five of the baseline 2 phase, the subject reported experiencing flu symptoms including headaches and vomitting. For the baseline 1 phase there were no comments coincident with days 10 or 13 which showed dips on the calmness and alertness factors respectively. For the evening series (Figure 4-1-2) the troughs, apparent in the baseline 2 phase on days four and five, coincided with the reported flu symptoms. There were no reported comments to coincide with the dip in the calmness factor on placebo phases. A domestic dispute was noted on day 2 of the baseline 1 recordings which may relate to the dip in the contentedness factor.

There was considered to be an absence of dramatic and consistent effects, within this subject, to meet the criteria for visually analysis of change (Kazdin, 1982; Parsonson & Baer, 1978). The presence of the one to two day dips in mood ratings could not be meaningfully related to intervention effects associated with tryptophan or placebo conditions.

Figure 4-1-1

FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 01

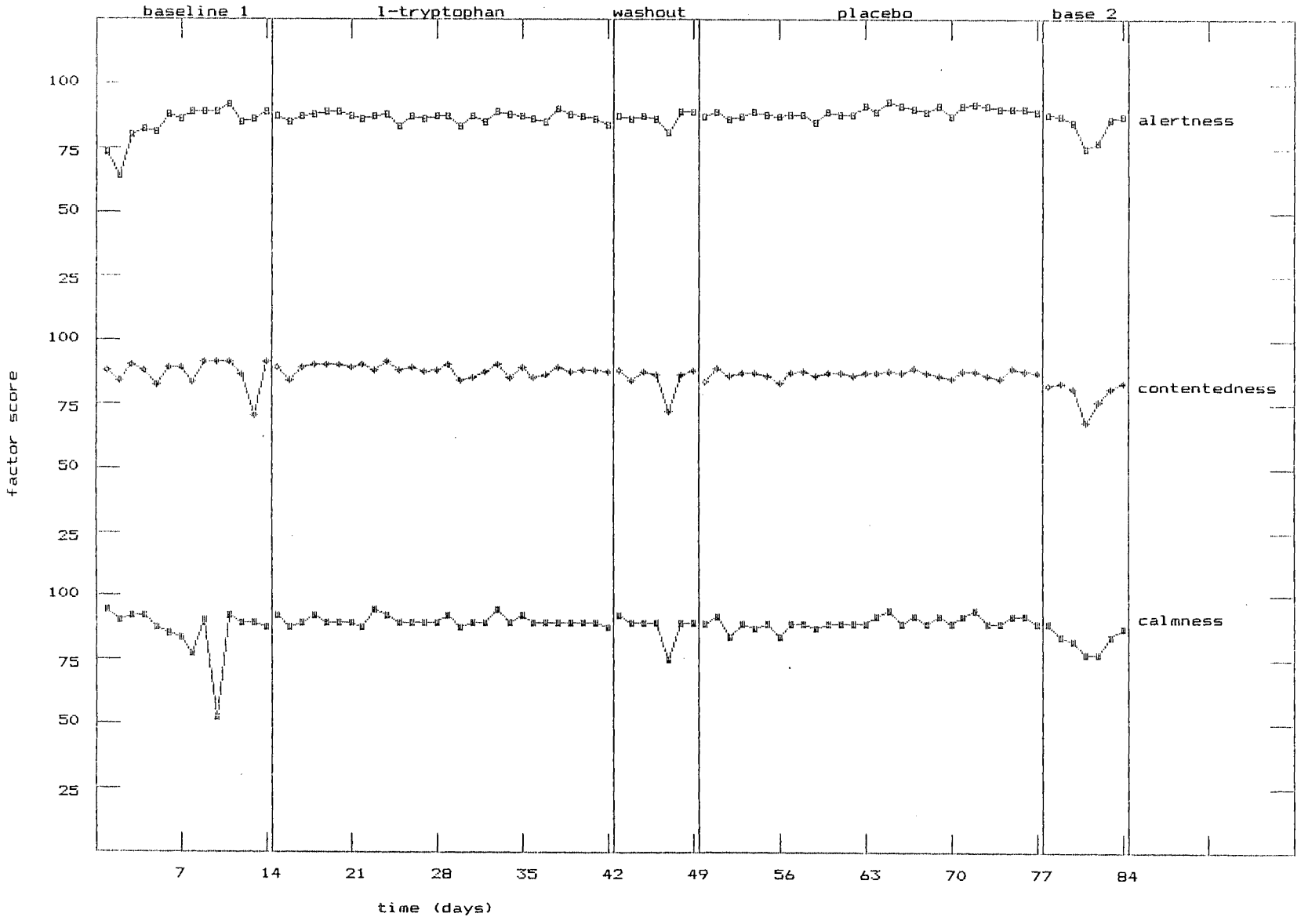
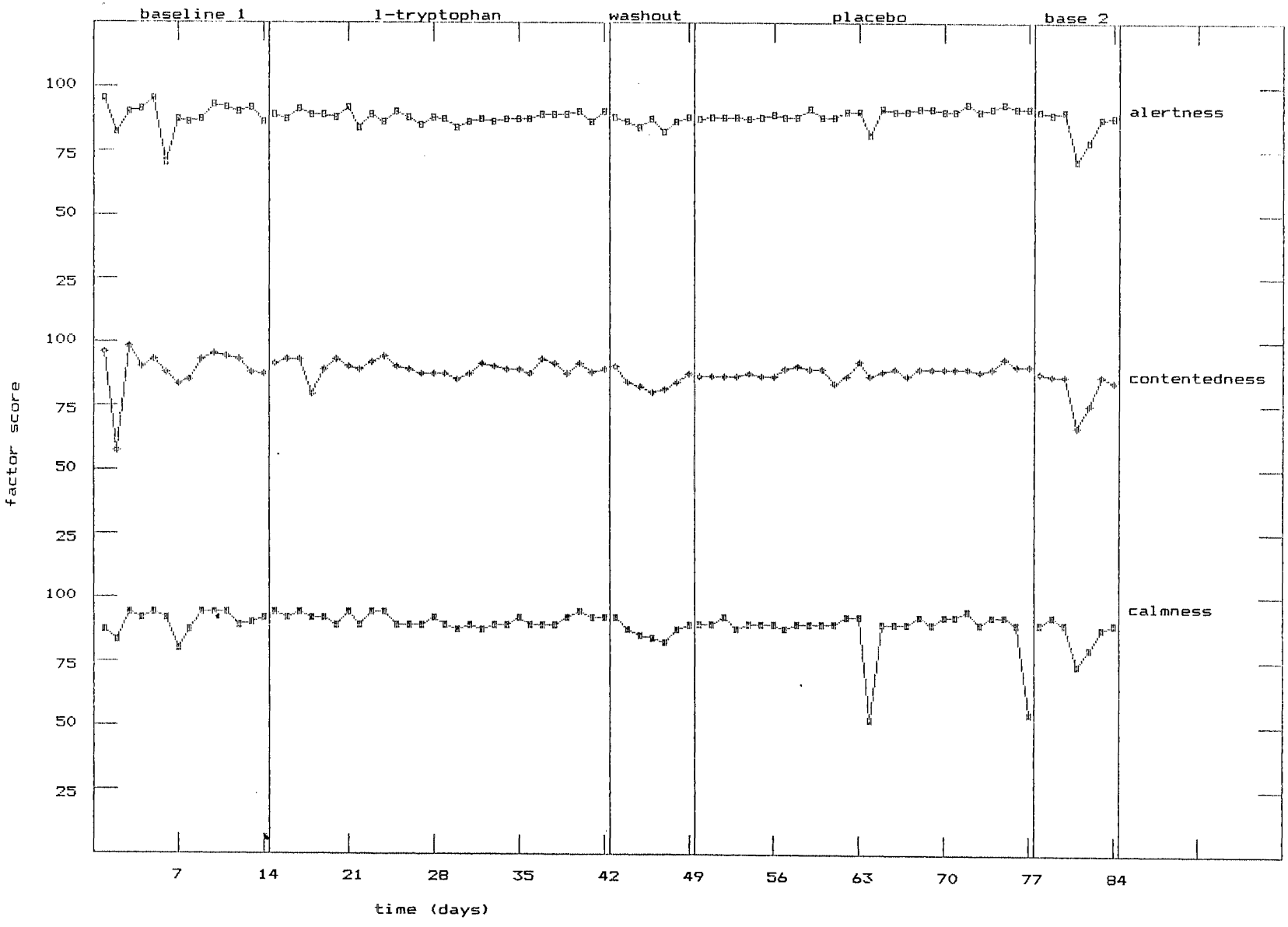


Figure 4-1-2

FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 01



Autocorrelation (rk) estimates

Estimations were calculated within phases for morning, evening and combined series for this subject.

Table 4-1-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=28)				wash(n=7)
	r1	r2	r3	r1	r2	r3	r4	r1
alertness								
morning	.58**	.28	.24	.01	-.01	-.24	-.18	-.13
evening	-.18	-.01	-.01	-.12	.34*	.12	.19	-.03
cont...ss								
morning	-.17	-.23	-.02	.01	.14	.10	.12	-.17
evening	-.32	.02	-.16	.07	-.27	.01	.04	.27
calmness								
morning	-.15	.21	-.02	-.17	-.09	-.13	-.02	-.13
evening	.16	-.37	-.38	.28*	.29*	.08	.17	.25

Table 4-1-3 continued:

factor	placebo(n=28)				bs2(n=7)
	r1	r2	r3	r4	r1
alertness					
morning	.34*	.41**	.38*	.16	.34
evening	.17	.23	.38*	.24	.18
cont...ss					
morning	-.10	-.23	-.03	.18	.19
evening	.24	.03	.28*	-.05	.15
calmness					
morning	.08	.28*	.21	.40	.34
evening	-.04	-.08	-.04	-.04	.28

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

Table 4-1-4 rk(k=less of N/4or4) values for combined morn. & eve. series

factor	baseline1(n=28)				tryptophan(n=56)				wash(n=14)		
	r1	r2	r3	r4	r1	r2	r3	r4	r1	r2	r3
alert..	-.16	.32*	-.03	.19	.10	.01	-.04	.24	.19	.06	.10
cont..	.01	-.27	-.09	-.01	.04	.11	-.12	-.09	.36*	.04	.05
calm..	-.14	-.01	-.15	.21	-.02	.15	-.14	.17	.43*	-.02	.01

Table 4-1-4 continued:

factor	placebo(n=56)				base2(n=14)		
	r1	r2	r3	r4	r1	r2	r3
alert..	.23*	.25*	.18	.31	.52**	.26	-.13
cont..	.10	.21	-.08	.06	.47*	.18	-.40
calm..	-.07	-.02	.01	-.04	.41*	.34	-.09

* exceeds the critical value for the .05 level of significnce

** exceeds the critical value for the .01 level of significance

t test results

Table 4-1-5 t test values for mean differences between baseline 1, tryptophan and placebo phases

alertness	base1 - tryp	base1 - plac	tryp - plac
morning	-1.43 ns	-2.57* +	-4.83** +
evening	-0.90 ns	-0.67 ns	-2.81** +
combined	-0.12 ns	-3.19 ** +	-5.12** +
contentedness			
morning	-0.74 ns	-0.29 ns	2.48*
evening	-0.19 ns	-0.21 ns	1.76 ns
combined	-0.64 ns	0.14 ns	2.79**
calmness			
morning	-1.38 ns	-1.38 ns	0.00 ns
evening	-0.51 ns	1.28 ns	1.81 ns
combined	-1.44 ns	-0.31 ns	1.72 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

\+ sig. t values affected by sig. levels of autocorrelation

\- indicates the first mean of the pair is the lowest

Comment on t test results

Significantly lower means for tryptophan versus placebo were demonstrated on alertness. The finding was maintained across comparisons of morning, evening and combined phases. However, as indicated from Table 4-1-5, significant levels of positive autocorrelation were indicated for placebo phases in all of these series and for the tryptophan phase in the evening series. Thus, significance levels for these t tests are likely to have been overestimated. The significance levels for alertness between baseline 1 and placebo phases (morning + combined series) are also threatened by the presence of significant positive autocorrelation. The level of contentedness was significantly higher for tryptophan than placebo in the morning and combined series and these estimates were free from autocorrelation bias. However, the magnitude of difference in means was small in both cases, i.e. for the morning series the tryptophan mean was 87.93 and placebo was 86.79 and for the combined series the respective means were 88.61 and 87.39.

C statistic results

Table 4-1-6 Z values for morning, evening and combined series

series	base1	base1+tryp	placebo	bs2	plac+bs2
morning					
alertness	2.743 **	~2.677 **	1.963 ns	-	-
cont...ss	-.577 ns	-.551 ns	-.179 ns	-	-
calmness	-.517 ns	-.251 ns	.467 ns	-	-
evening					
alertness	-.512 ns	-.831 ns	1.120 ns	-	-
cont...ss	-1.201 ns	-1.582 ns	1.484 ns	-	-
calmness	.764 ns	1.589 ns	.961 ns	-	-
combined					
alertness	-.561 ns	-.513 ns	1.857 ns	2.207 ns	5.002 **
cont...ss	.032 ns	.189 ns	1.133 ns	1.935 ns	5.321 **
calmness	-.702 ns	-.596 ns	1.048 ns	1.892 ns	.464 ns

** exceeds the critical value for the .01 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see Chapter III for explanation)

Comment on C statistic results

As is evident from Table 4-1-6, the presence of a significant trend was established for the alertness dimension within the baseline 1 phase of the morning series. This necessitated calculation Z for the baseline1 + tryptophan phases to be based on a less powerful procedure, which only used the first half of the tryptophan phase. On this basis a significant departure in trend for tryptophan alertness relative to baseline was demonstrated. Significant changes in trend were also indicated for baseline 2 phases relative to placebo, on alertness and contentedness, for the combined series.

(c) Hours of sleep

Table 4-1-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=28)				placebo(n=28)			
r1	r2	r3	r1	r2	r3	r4	r1	r2	r3	r4
-.07	.09	-.34	-.07	-.002	.27	-.24	-.13	.02	.04	.09

None of the above estimates proved significant

t test value results for hours of sleep

base1 - tryp	tryp - plac	base1 - plac
-0.002 ns	1.28 ns	1.04 ns

C-statistic results (Z values)

baseline1	tryptophan	base1+tryptophan	placebo
.314 ns	-.261 ns	-.600 ns	-.701 ns

Comment on hours of sleep

No significant changes emerged for hours of sleep in terms of the mean difference (t) between baseline 1 and tryptophan phases, baseline 1 and placebo phases or tryptophan versus placebo periods. In addition no significant trends were observed in any of the above phases.

(d) Side effects

The baseline 1 phase was free of any reported side effects. Similarly, the first two weeks of the tryptophan phase showed an absence of reported effects until day 14 when the subject described symptoms such as flushing and pulsating - in keeping with the niacin reaction (Chapter II). The remainder of the tryptophan phase in addition to the placebo and baseline 2 phases were free of reported side effects while the symptoms noted on day four of the baseline 2 phase coincided with the reported flu experience at this time.

(5) Summary and Conclusions

Visual evaluations, indicating an absence of significant effects within and across mood factors, were corroborated by statistical findings except for two points of departure. Significantly higher mean values for tryptophan over placebo phases (for both morning and combined series) for the contentedness dimension were indicated statistically but were not supported visually and were not indicated relative to baseline. Also, the magnitude of difference between the respective means was small. Similarly, a significant departure in trend for alertness scores in the morning tryptophan versus baseline 1 phase was statistically but not visually apparent. Due to the baseline 1 trend, the calculation was based on a less powerful application of the C statistic, which used only the first half of the tryptophan phase. As is evident from Table 4-1-5, there was a non significant mean difference between these two phases.

Measures on the weekly scores remained quite consistent throughout the trial with elevation in the final HSCL rating probably associated with the reported flu experience. Similarly, there was no evidence for changes with respect to total hours of sleep between baseline 1, tryptophan and placebo phases.

One noticeable change which could be attributed to tryptophan administration concerns symptoms reported on day 14 of the tryptophan phase which parallel closely effects frequently reported in association with the niacin reaction (Chapter II).

This subject was the only one to report such a dramatic effect. It could be speculated that a dose of 6gms for 28 days in a subject below the desirable weight for height range could have been responsible for such a reaction. However, no other significant increases in the incidence of reported side effects or subjective complaints support this possibility. Thus, consumption of 6gms/day of tryptophan for 28 days was not associated with consistent or dramatic changes on any of the psychological measures relative to placebo or baseline periods.

4.2.2 Subject 02

(1) Demographic variables:

age(yrs): 37 sex: male height(cms):168
weight(kgs):64.00
(within desirable weight range)

drug consumption: high nicotine + caffene intake

l-tryptophan experience: - not consumed prior to this trial

motivation for participation: - depression

(2) Psychological variables

(a) Depression status

This subject could not be classed as depressed on the basis of the initial SDS score, if Zung's depressive categorization is considered, although subsequent SDS scores throughout the study reached the mild - moderate category (Zung, 1972). Initial and subsequent scores exceeded 1 SD above the mean with respect to Knight et al.'s (1983) norms. Given a depression motivation for participation and the fact that consumption of prescribed doses of antidepressants and hypnotics (i.e. 50 mg clomipramine + 2mg lorazepam/day) continued throughout the trial, this subject was classified as depressed.

(b) Anxiety status

With respect to Knight et al.'s (1983) norms, this subject exhibited an initial Trait anxiety score exceeding 1 SD above the mean for the appropriate age and sex category, while initial and several subsequent State scores exceeded 2 SD's above the mean. Thus, this individual was considered to be experiencing moderate levels of anxiety.

(3) Experimental variables

(a) Dose level(gms/day): 6

(b) Phase description

baseline 1	placebo	washout	tryptophan	baseline 2
14days	28days	7days	11days	3days

(c) Extra details

This subject was the only one to complete the placebo phase prior to tryptophan. Scale completion time was consistent from day to day (i.e. within 2 hours). Evening scales were completed on returning home from work. Only two moodscale ratings were missed. This subject expressed the desire to withdraw from the program after the 11th day of the tryptophan phase due to the lack of any beneficial effects. Following this decision, 3 days of the baseline 2 phase were completed before trial termination.

(4) Results and analysis

(a) Weekly scores

Table 4-2-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			placebo				wash	tryptophan	
day	01	07	14	21	28	35	42	49	56	63
zung	38	34	37	32	40	30	31	31	40	42
state	47	36	53	42	46	34	41	35	43	39
HSCL	71	73	88	90	93	83	84	87	94	100

Table 4-2-2 HSCL factor scores

	baseline 1				placebo			wash	tryptophan	
day	01	07	14	21	28	35	42	49	77	84
factor										
1	1.40	1.22	1.66	1.39	1.31	1.41	1.22	1.30	1.39	1.55
2	1.54	1.27	1.75	2.17	2.43	2.02	2.04	2.41	2.45	2.28
3	1.00	1.16	1.34	1.50	1.60	1.34	1.34	1.34	1.52	1.34
4	1.10	1.10	1.56	1.09	1.29	1.29	1.28	1.38	1.29	1.76
5	1.15	1.42	1.44	1.86	1.46	1.42	1.58	1.61	1.59	1.62

Comment on weekly scale scores

This subject maintained relatively high SDS and State anxiety scores throughout all trial phases. There was an increase in HSCL total scores as the trial proceeded with the two highest ratings during the tryptophan phase. As evident from Table 4-2-2, the greatest increases seemed related to the HSCL factors 2, 4 and 5 i.e. obsessive compulsive, depression and anxiety respectively. In relation to Derogatis et al.'s (1974) normative data for these factors (Table 3-4), the present subject's score on 'obsessive-compulsive' lies closest to the anxious neurotic group with the last three scores tended closer to the depressed neurotic's mean. The 'depression' and 'anxiety' dimensions tend to drift from scores in keeping with the normals means to values closer to the anxious neurotic means.

(b) Mood factors

Visual analysis of graphed data

No dramatic trends or changes in level were apparent either within or across phases following visual inspection of morning and evening series (Figures 4-2-1 & 4-2-2). A slight increasing trend within the morning baseline 1 phase for the alertness and contentedness dimensions was detected. Flu symptoms were reported during the first four days of baseline 1 which may account for depressed scores at this time. A high level of day to day variability was exhibited across all phases in both series. Marked declines in the alertness dimension for the evening scale

Figure 4-2-1

FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 02

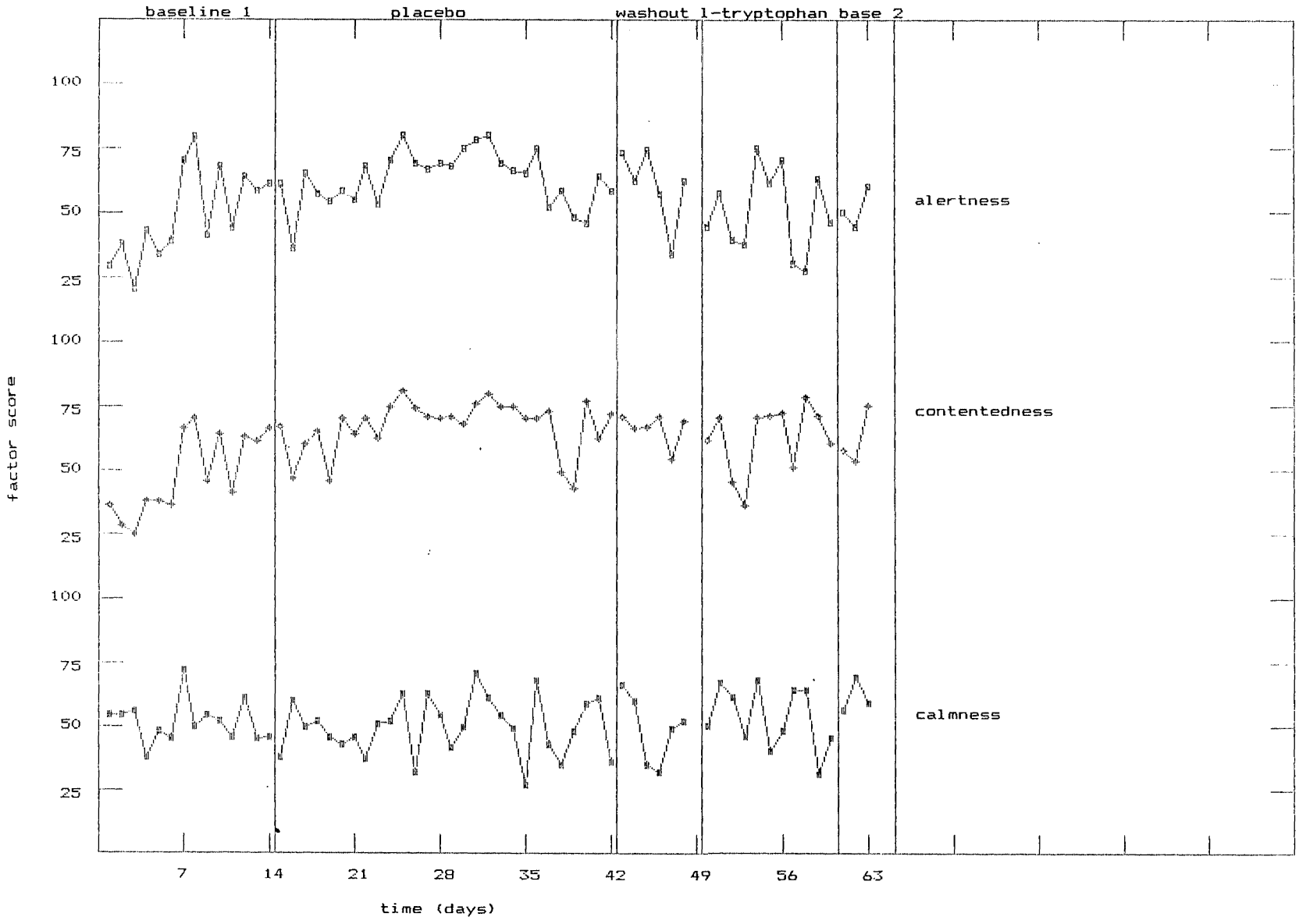
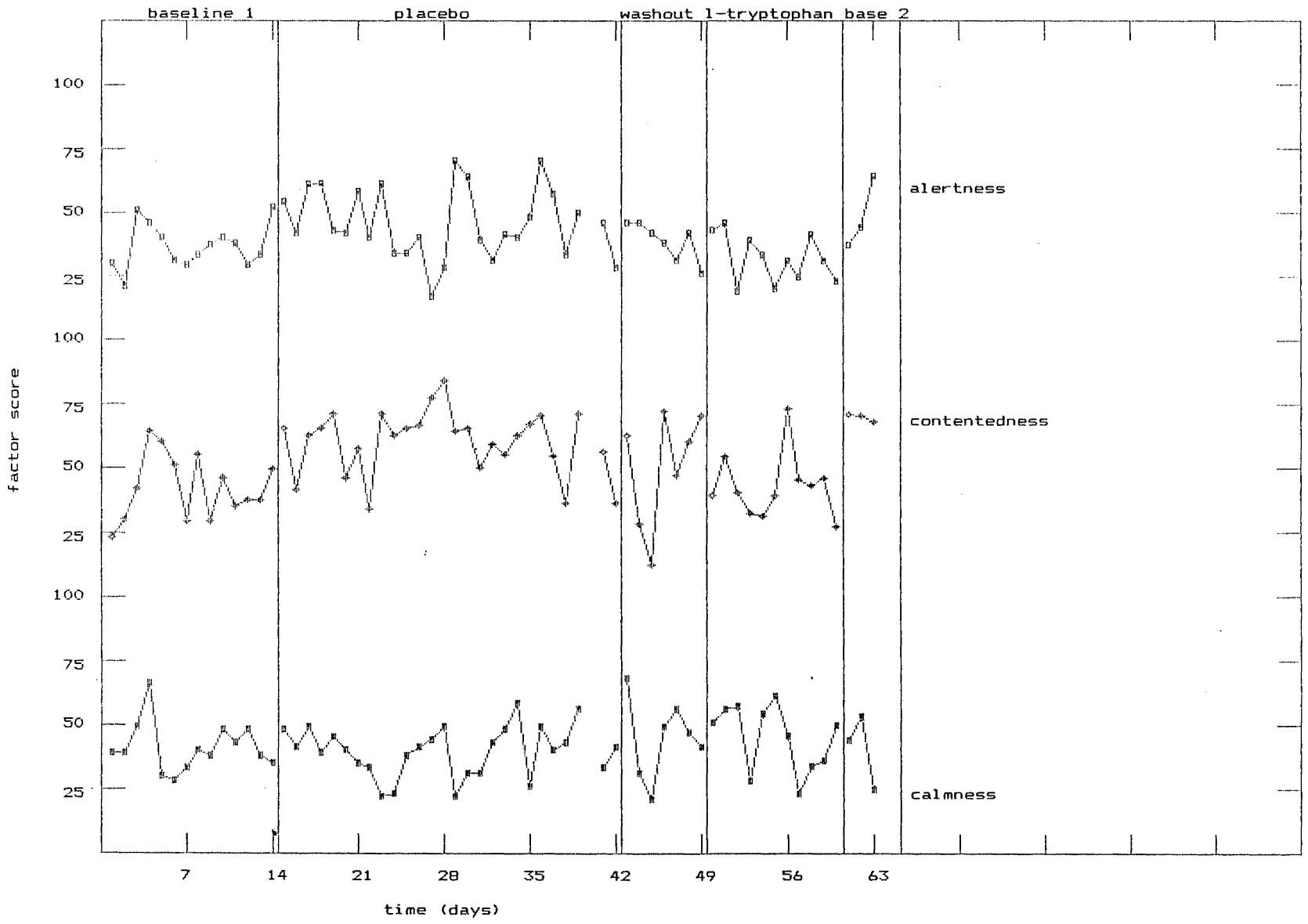


Figure 4-2-2

FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 02



relative to the morning series were apparent.

Autocorrelation estimates

Table 4-2-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			placebo(n=28)				tryp(n=11)	
	r1	r2	r3	r1	r2	r3	r4	r1	r2
alertness									
morning	.26	.34*	.07	.37*	.36*	.30	.12	-.04	-.30
evening	.06	-.41	-.30	.17	-.26	-.05	-.19	-.19	-.16
cont...ss									
morning	.45*	.35*	.12	.24	.16	.21	.01	.05	-.32
evening	.13	.05	-.46	.05	.02	-.07	.07	.02	-.24
calmness									
morning	-.25	.01	-.33	-.19	-.16	-.03	.11	-.15	-.34
evening	.14	-.30	-.33	.13	.14	-.14	-.29	.17	-.30

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Table 4-2-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - plac	base1 - tryp	plac - tryp
alertness			
morning	~-2.73 *+	-0.11 ns	~ 2.47 *+
evening	-2.27 *	1.23 ns	3.03 **
contentedness			
morning	~-4.06 **+	-2.49 *+	0.49 ns
evening	-4.28 **	-0.14 ns	3.78 **
calmness			
morning	0.60 ns	-0.39 ns	-0.84 ns
evening	0.45 ns	-0.91 ns	-1.46 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

+ sig. t values affected by sig. levels of autocorrelation

- indicates the first mean of the pair is the lowest

~ phase variances unequal,t-test approximation used (see Chapter III)

Comment on t test results

As is evident from Table 4-2-4, significant findings, free from autocorrelation bias, were limited to the evening series. For the alertness and contentedness dimensions, the placebo phase exhibited a significantly greater mean than the baseline and tryptophan phases. In neither case, was there a significant difference between baseline and tryptophan phases. The remaining significant t test outcomes (morning series) are likely to have been overestimated due significant levels of positive autocorrelation within the phases concerned.

C statistic results

Table 4-2-5 Z values for morning and evening series

series	base1	bs1+plcb	plcb+wash	(plcb+wash)+tryp
morning				
alertness	1.35 ns	3.22 **	2.08 *	~-0.02 ns
cont...ss	2.11 *	~ 0.01 ns	1.37 ns	1.25 ns
calmness	-0.92 ns	-1.05 ns	-0.77 ns	-0.85 ns
evening				
alertness	0.80 ns	1.95 *	1.11 ns	2.00 *
cont...ss	0.94 ns	2.72 **	0.67 ns	2.33 **
calmness	0.65 ns	0.85 ns	0.76 ns	1.23 ns

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see Chapter III for explanation)

Comment on C statistic results

As evident from the Table 4-2-5, presence of significant trends in the morning series for ' baseline contentedness' and '(placebo + washout) alertness' meant that respective comparison with the morning series 'placebo contentedness' and 'tryptophan alertness' were based on the less powerful C statistic application (see Chapter III for explanation). A significant departure was indicated in the morning for the placebo phase relative to baseline on the dimension of alertness. Secondly, in

the evening, significant departures for placebo over baseline and trytophan over (placebo+washout) were indicated for alertness and contentedness dimensions.

(c) Hours of sleep

Table 4-2-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=11)		placebo(n=26)				tryptophan(n=11)	
r1	r2	r1	r2	r3	r4	r1	r2
-.16	.11	-.15	-.12	-.03	-.05	-.31	.11

None of the above estimates prooved to be significant

t test results for hours of sleep

base1 - plac	base1 - tryp	plac - tryp
3.13 **	4.89 **	~ 0.65 ns

Comment on hours of sleep

As is evident from the above t-test results, the mean hours of sleep during both placebo and tryptophan phases tended to be significantly lower ($p<.01$) than the tryptophan phase while no significant difference was apparent between the placebo and tryptophan periods. Results were free from autocorrelation bias.

(e) Side effects

Table 4-2-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)		placebo(n=27)				tryptophan(n=11)	
r1	r2	r1	r2	r3	r4	r1	r2
.17	-.39	.10	.29*	-.01	.14	.30	-.16

* exceeds the critical value for .05 level of significance

t test results for severity of side effects

base1 - plac	base1 - tryp	plac - tryp
-3.32 **	-6.84 **	-4.59 **

Comment on side effects

A systematic increase in the severity of symptoms was observed throughout the trial with the most severe levels reported during the tryptophan phase. Mean severity values were significantly higher during placebo and tryptophan phases relative to baseline 1 and the tryptophan phase proved to be significantly greater than the placebo phase. In both cases the t value was particularly high, which may have counteracted the autocorrelation bias associated with the placebo phase. The only effect to appear with notable increase during the tryptophan phase, was described by the subject as 'hot flushes'. This effect was only reported on one occasion during the series prior to tryptophan ingestion but appeared frequently during the tryptophan and three days of the baseline 2 period. It could be speculated that this effect resembled symptoms associated with the 'niacin reaction' (described in Chapter II).

(5) Summary and Conclusions

Analysis for this subject focused on detection of antidepressant effects given the motivation for participation as 'depression' and the tendency for elevation in some Zung scores throughout the trial. No noticeable effects could be detected on the basis of visual analysis of daily mood ratings. The visual indication of slight trends in the morning baseline phase for alertness and contendedness was only supported by a significant C statistic result in the latter case.

Significant t test outcomes (free from autocorrelation) were limited to higher placebo means (relative to baseline and tryptophan phases) for alertness and contentedness dimensions on the evening series but were not supported by visual analysis. These findings were not considered particularly meaningful or relevant to the determination of tryptophan's antidepressant or general mood - altering effects, particularly since there were no baseline - tryptophan differences.

In the case of C statistic applications, attention was directed to the detection of changes in trend between (1)baseline

and placebo phases and (2)(placebo+washout) and tryptophan phases. In the first case, significant changes were detected in the morning for alertness and in the evening for alertness and contentedness. In the second case significant departures were noted on alertness and contentedness in the evening. Visual analysis was not supportive of these findings.

The findings of slight visual and statistical (t test) increases in placebo relative to baseline phases on alertness and contentedness and apparent declines during tryptophan intake relative to (placebo+washout) phases were not psychologically meaningful. The decline in alertness for the tryptophan relative to placebo phase is in keeping with tryptophan's reputation for increasing drowsiness. The significant reduction in hours of sleep for tryptophan relative to baseline was not maintained relative to placebo.

The most striking result for this subject concerned the increased experience of negative side effects during the tryptophan relative to baseline and placebo phases. This increase tended to be supported by increasing HSCL scores which also peaked during the tryptophan phase. The absence of clear antidepressant effects in this subject may be attributable to the brevity of the tryptophan phase. In addition, it is conceivable that the 6gms/day dosage in this subject was too high in combination with his standard antidepressant medication.

4.2.3 Subject 03

(1) Demographic variables

age(yrs): 33 sex: female height(cms):169
weight(kgs):65.00
(within desirable weight range)

chemical contraceptives: yes
PMT: yes

l-tryptophan experience: - not consumed prior to this project
motivation for participation: - depression

(2) Psychological variables

(a) Depression status

On the basis of the initial SDS total score this subject was classed as moderately depressed (Zung, 1972). According to Knight et al.'s (1983) norms this score exceeded one standard deviation above the mean for the appropriate age and sex category. Relatively high subsequent SDS scores were maintained throughout the trial.

(b) Anxiety status

With respect to Knight et al.'s (1983) norms, this subject exhibited a Trait score (56) well in excess of one standard deviation above the mean for her age category. The initial State score was within one SD from the mean. However, three subsequent scores reached 60 in contrast to the mean for this age group of 34.47 (Knight et al., 1983). Consequently this subject was considered to be experiencing reasonably high levels of anxiety.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	28days	7days	14days	7days

(c) Extra details

Scale completion time was regular (within two hours from day to day). No missing data was accrued for the moodscales. Weekly ratings for the Zung, State anxiety and HSCL scales were missed on the last week of baseline 1 and at the end of baseline 2. Otherwise participation continued, uninterupted for the 70 day trial with placebo ingestion forgotten on one night.

(4) Results and analysis

(a) Weekly scores

Table 4-3-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan				wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56	63	70
scale											
zung	49	52	-	52	45	48	52	44	43	52	-
state	43	53	-	60	60	36	60	45	46	53	-
HSCL	102	123	-	123	118	107	113	101	96	118	-

Table 4-3-2 HSCL factor scores

	baseline 1			tryptophan				wash	placebo	
day	01	07	14	21	28	35	42	49	56	63
factor										
1	1.27	1.48	-	1.54	1.48	1.44	1.31	1.87	1.34	1.99
2	1.95	2.58	-	2.31	2.60	1.94	2.14	1.31	1.85	2.22
3	1.73	2.98	-	2.98	2.44	2.50	2.89	1.93	1.50	2.05
4	1.60	2.62	-	2.70	2.17	2.16	2.60	2.19	2.04	2.44
5	2.18	1.77	-	1.62	2.02	1.77	1.74	1.72	1.87	1.73

Comment on weekly scale scores

As evident from Table 4-3-1, relatively high Zung and State total scores were maintained throughout the trial with no decline during the tryptophan phase. High total HSCL scores were maintained throughout the series. There was a slight decline in HSCL total scores during the tryptophan, washout and first week of the placebo phase. HSCL factor scores were closer to means for depressed and anxious groups rather than normals (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

No dramatic or meaningful changes with respect to Kazdin's (1982) proposed criteria for visual evaluation were apparent

Figure 4-3-1
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 03

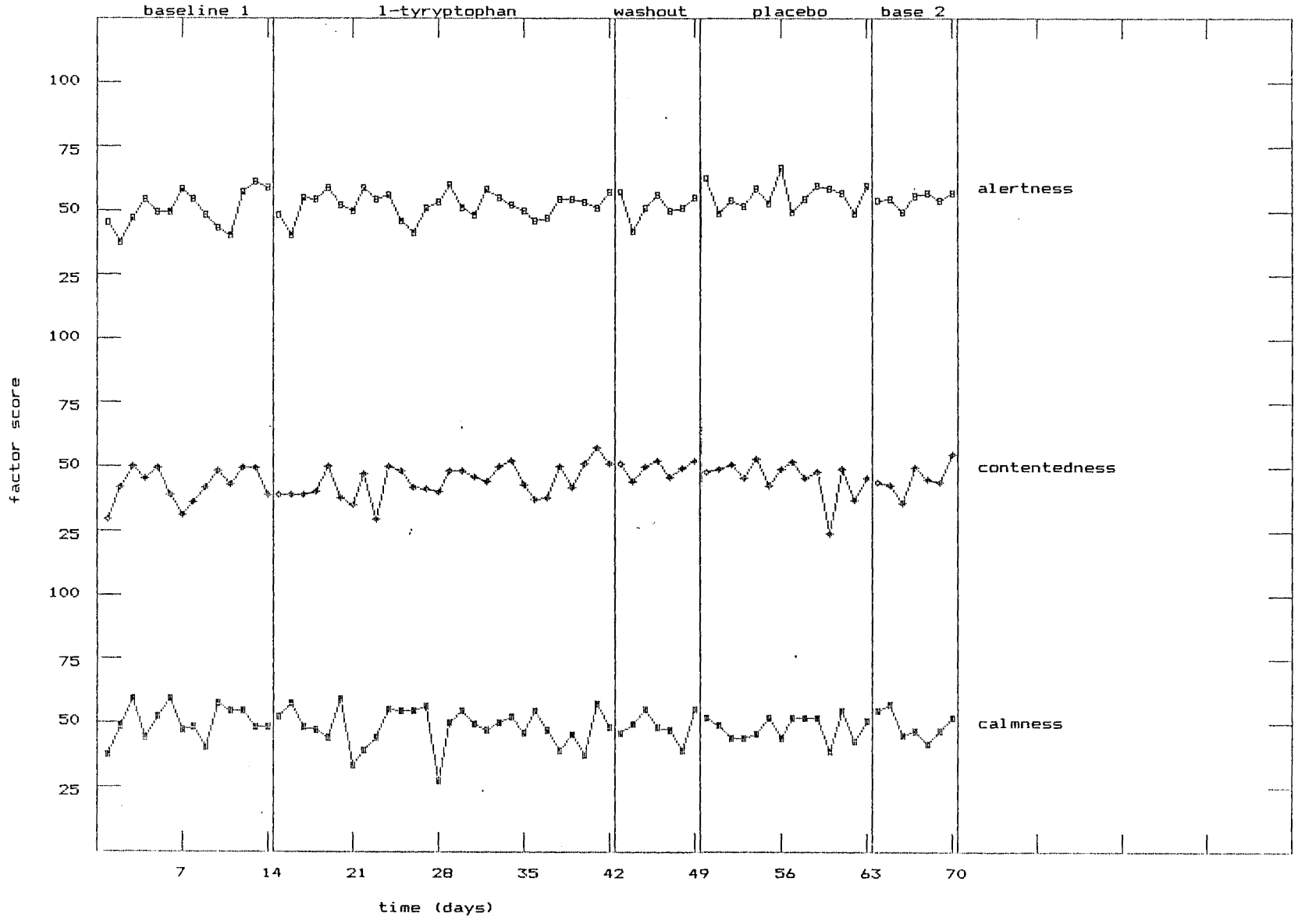
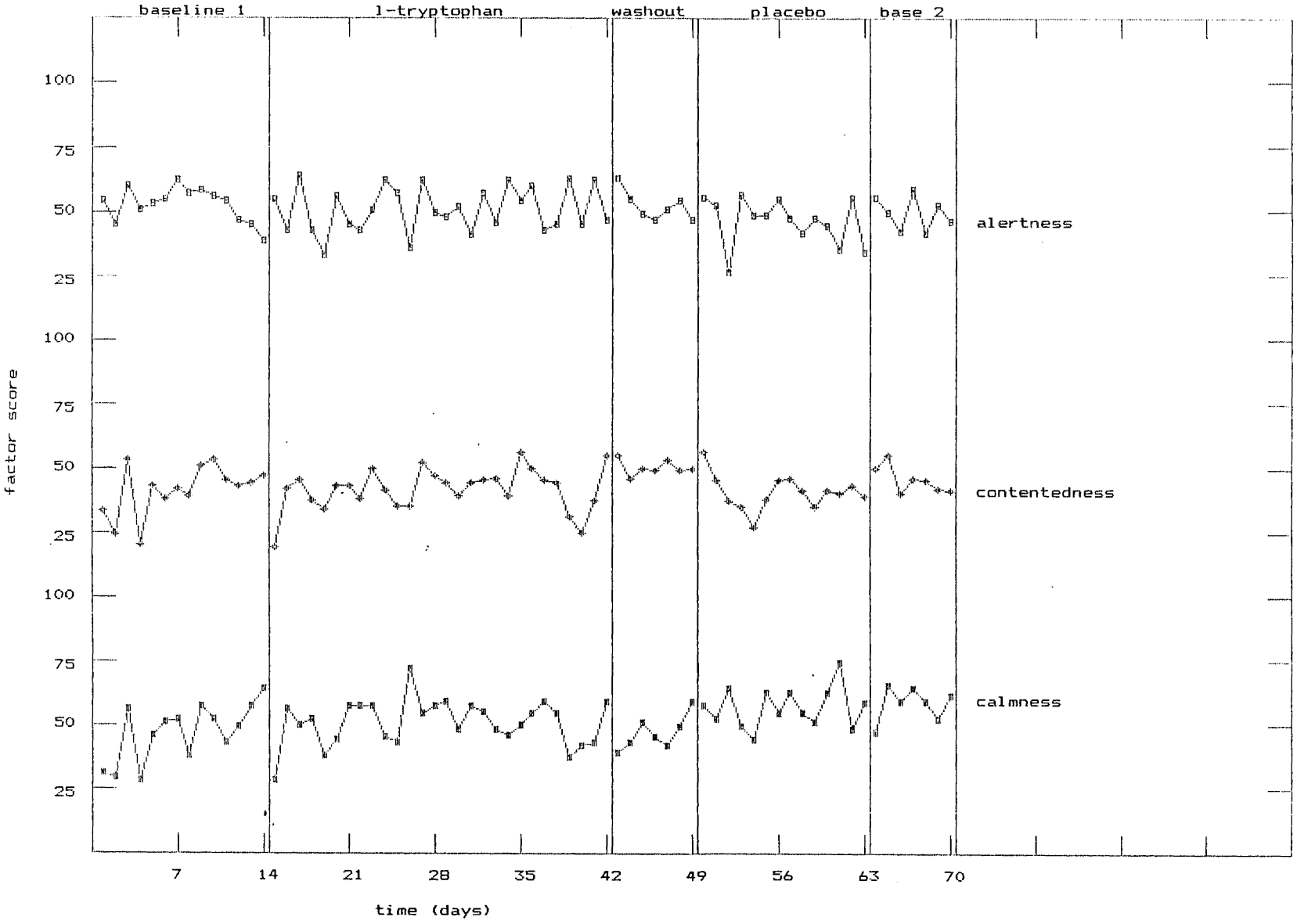


Figure 4-3-2
FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 03



either within or across phases for the morning (Figure 4-3-1) or evening (Figure 4-3-2) series. There was some indication of greater day to day variability for the evening series relative to morning ratings.

Autocorrelation estimates

Table 4-3-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=28)			
	r1	r2	r3	r1	r2	r3	r4
alertness							
morning	.45*	-.24	-.36	.18	-.20	-.32*	-.16
evening	.31	.29	-.04	-.36*	-.02	.10	-.10
cont...ss							
morning	.27	-.21	-.28	.14	.01	.06	-.12
evening	-.15	.34	.10	.16	-.21	-.86	.05
calmness							
morning	-.12	-.30	-.02	-.09	-.12	-.19	-.09
evening	.04	.02	.22	.04	-.12	-.15	.06

Table 4-3-3 continued:

factor	placebo(n=14)		
	r1	r2	r3
alertness			
morning	-.42	.05	-.25
evening	-.39	-.05	.22
cont...ss			
morning	-.18	.37	-.14
evening	.32	-.20	-.47
calmness			
morning	-.45	.18	-.27
evening	-.24	-.24	-.11

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Table 4-3-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	~-0.85 ns	-2.51 *+	-2.54 *+
evening	0.64 ns	-1.61 *	~-2.42 *+
contentedness			
morning	-0.87 ns	-1.34 ns	-0.78 ns
evening	-0.14 ns	0.16 ns	0.35 ns
calmness			
morning	0.68 ns	0.65 ns	-2.15 *
evening	-1.29 ns	-2.67 *	-2.06 *

* exceeds critical value for the .05 level of significance

+ sig. t values affected by sig. levels of autocorrelation

- indicates the first mean of the pair is the lowest

~ phase variances unequal,t-test approximation used (see Chapter III)

Comment on t test results

Significant findings were limited to the alertness and calmness dimensions for this subject. The mean for the placebo phase on the alertness dimension was found to be higher than baseline in the evening series. For the calmness dimension, the placebo mean was significantly higher than baseline in the evening and higher than tryptophan in the morning and evening series. In the cases of the tryptophan - placebo differences on alertness the presence of significant negative autocorrelation during the tryptophan phase may have led to a conservative estimate (Hartmann et al., 1980) of t test significance, thus, the elevation of the placebo mean relative to tryptophan in both series should probably be considered as a valid result. The presence of positive autocorrelation during the morning baseline phase for alertness is more likely to have led to a liberal bias of t test significance between baseline and placebo phases in the morning and consequently must be treated cautiously.

C statistic results

Table 4-3-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	1.99 *	~-0.36 ns
cont...ss	1.69 *	~-0.06 ns
calmness	0.10 ns	-0.32 ns
evening		
alertness	1.94 *	~ 1.99 *
cont...ss	-0.46 ns	0.23 ns
calmness	0.81 ns	0.39 ns

* exceeds the critical value for the .05 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see section Chapter III for explanation)

Comment on C statistic results

As is evident from the Table 4-3-5, significant trends were detected in the baseline phases for alertness (morning and evening) and contentedness (morning only). Subsequently, a significant departure in the tryptophan relative to baseline phase was limited to the evening ratings on alertness. This calculation here was based on the less powerful application of the C statistic which effectively involved comparison of the baseline with only the first half of the tryptophan phase.

(c) Hours of sleep

Table 4-3-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=1			tryptophan(n=28)				placebo(n=14)	
r1	r2	r3	r1	r2	r3	r4	r1	r2
-.53*	-.02	.37*	-.34*	.04	-.21	.01	-.15	-.19

* exceeds the critical value for the .05 level of significance

t test value results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
-0.25 ns	~-2.19 *+	~-2.12 *+

* exceeds the critical value for the .05 level of significance

~ t-test approximation used due to unequal phase variances

+ sig. t values affected by sig. levels of autocorrelation

Comment on hours of sleep

As indicated from the t test results, mean hours of sleep tended to be significantly lower during the baseline and tryptophan phases relative to the placebo period. The presence of significant negative autocorrelation during the baseline and tryptophan phases is more likely to have caused an underestimation of significance, therefore, the significance of the above t tests can be interpreted relatively confidently.

(d) Side effects

Table 4-3-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=28)				placebo(n=14)	
r1	r2	r3	r1	r2	r3	r4	r1	r2
.16	-.06	-.14	-.08	-.01	.01	-.26	.24	-.15

None of the above estimates proved significant

t test value results for severity of side effects

base1 - tryp	base1 - plac	tryp - plac
-2.07 *	-2.33 *	-0.12 ns

* exceeds the critical value for the .05 level of significance

Comment on side effects

A significant increase in side effects was noted for the tryptophan and placebo periods relative to baseline, while the tryptophan phase demonstrated no significant elevation with respect to placebo. Symptom severity was characterized by a sudden rise during the tryptophan phase (mean=4.0) relative to

baseline 1 (mean=2.79) which continued through the placebo period (mean=4.1) and only began to decline during the second baseline period (mean=3.6). Headaches were reported only once during baseline 1 and placebo periods but on 14 occasions during the tryptophan condition. The difference is still impressive despite the tryptophan phase being twice the length of the other two. Reports of abdominal cramps were limited to the first week of tryptophan ingestion.

(e) Premenstrual tension

Menstrual bleeding was first noted during days 1 and 2 of baseline 1, thus, the associated premenstrual period could not be considered. The only other period of menstrual bleeding commenced on the 4th washout day and continued for six days. In this case no obvious changes were detected with respect to graphed mood data, side effect severity or quality for the prementrual period. The increased level of symptoms reported for the tryptophan phase tended to be particularly concentrated in the first 2 weeks (prior to the premenstrual phase).

(5) Summary and Conclusions

As indicated previously the present subject was considered to be suffering from mild to moderate levels of depression and demonstrated high initial Trait and subsequent State anxiety levels relative to other participants. There was no indication of significant alleviation of such symptoms during the tryptophan phase. Visual and statistical analysis of mood scale data was not supportive of antidepressant, antianxiety or general mood elevating properties for tryptophan in this subject. The significantly lower means for alertness during tryptophan relative to placebo periods could not be supported by visual analysis and the reduction in alertness for the tryptophan phase was not significant relative to baseline. The detection of a significant departure for the evening tryptophan phase relative to baseline on the alertness dimension should be interpreted cautiously. Firstly, the less powerful C statistic application, employed here, meant only the first half of the tryptophan phase was considered, and secondly, the change was not supported by

visual analysis. The high daily variablity in mood ratings for this subject, as indicated from appraisal of Figures 4-3-1 and 4-3-2 acted to reduce the confidence placed in the above statistically significant outcomes.

The finding of significantly lower mean hours of sleep during the tryptophan phase relative to placebo was not considered particularly meaningful given that the baseline was also significantly reduced relative to placebo and that there was no difference between tryptophan and baseline periods. The severity of reported side effects for this subject demonstrated a marked elevation during the tryptophan relative to baseline phase. This elevation was also maintained througout the washout and placebo phases. Symptoms strongly associated with tryptophan ingestion were headaches and abdominal cramps.

Thus, tryptophan administration could not be associated with therapeutic benefit or general mood altering effects in this subject. The most dramatic effect tended to relate to the increased incidence of headaches and abdominal cramps during the tryptophan phase relative to other trial periods. The lack of therapeutic benefit may have been attributable to the the lower than recommended antidepressant dose (Chouinard et al., 1978) in this subject.

4.2.4 Subject 04

(1) Demographic variables

age(yrs): 30 sex: male height(cms):188

weight(kgs):78.00

(within desirable weight range)

vegetarian: yes

motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial SDS score for this subject was close to the mean for the appropriate age and sex category with respect to Knight et al.'s (1983) norms. Subsequent scores were either close to or below this mean. Consequently, on the basis of SDS ratings and a 'general interest' motivation for participation, this subject was classed as 'non depressed'.

(b) Anxiety status

With respect to Knight et al.'s (1983) norms, the Trait anxiety score was close to the mean for this subject. Similarly, the initial and most subsequent State anxiety scores were below the appropriate mean. Consequently, this subject was considered relatively free from symptoms of anxiety.

(3) Experimental variables

(a) Dose level(gms/day): 6

(b) Phase description

baseline 1	tryptophan
14days	14days

(d) Extra details

Scale completion time was regular with missing data confined to two consecutive days during the evening tryptophan phase. Participation was concluded earlier than expected for this subject due to his leaving Christchurch suddenly.

(4) Results and analysis

(a) Weekly scores

Table 4-4-1
Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan	
day	01	07	14	21	28
scale					
zung	32	32	27	26	25
state	25	28	25	30	27
HSCL	86	84	77	83	72

Table 4-4-2
HSCL factor scores

	baseline 1			tryptophan	
day	01	07	14	21	28
factor					
1	1.84	1.08	1.35	1.17	1.08
2	1.74	2.07	1.59	1.86	1.82
3	1.12	1.54	1.00	1.69	1.28
4	1.51	1.44	1.35	1.47	1.00
5	1.00	1.00	1.00	1.16	1.16

Comment on weekly scale scores

No dramatic differences were apparent between baseline and tryptophan phases for any of the weekly scales or HSCL factor scores. HSCL factor scores were close to the normal means (Table 3-4) according to Derogatis et al. (1974).

(b) Moodscale ratings

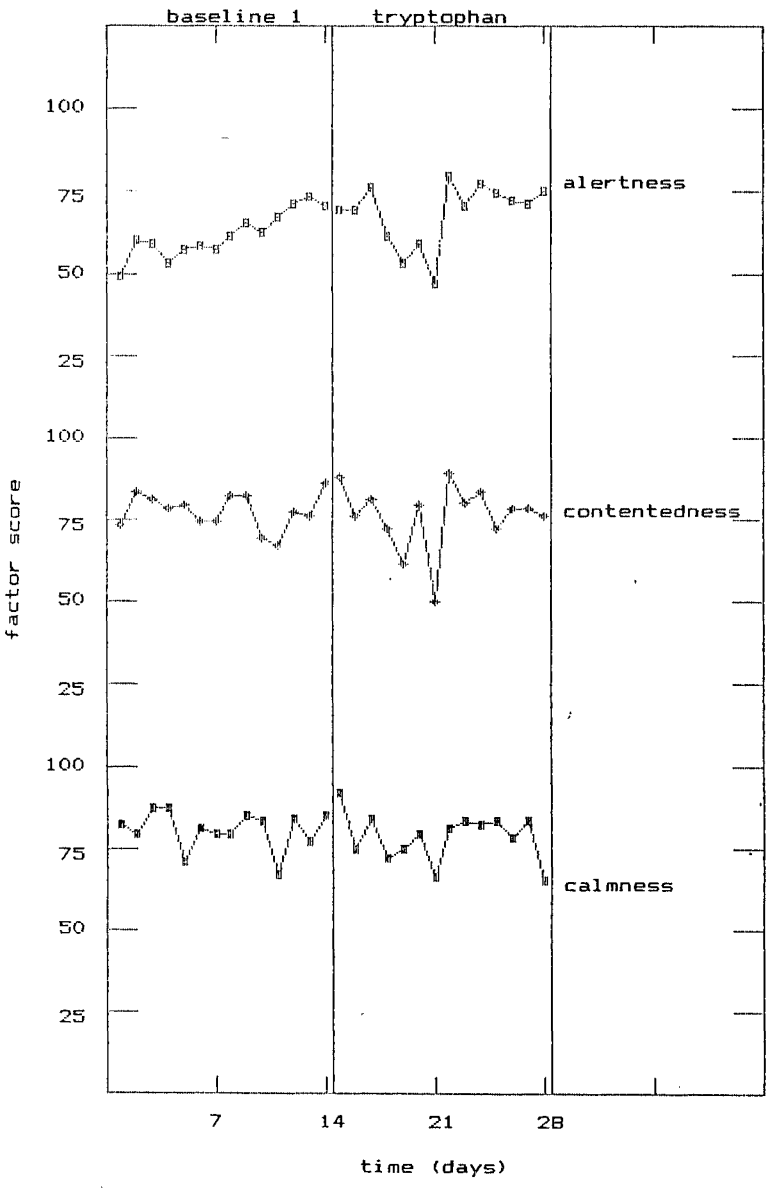
Visual analysis of graphed data

Graphs for both morning and evening series appear in Figure 4-4 for this subject. The most notable feature of the graphed mood scale data was the appearance of a consistently increasing trend during the baseline phase (particularly during the evening) for the alertness dimension. Subsequently, in both series there was a marked decline for the first few days of the tryptophan phase on the alertness dimension. There was also evidence of a decline in contentedness for the first few days of the tryptophan phase (relative to baseline) in both series, and some indication of the same pattern with respect to the calmness dimension for the evening series. The increasing trends in the baseline series for alertness probably tend to exaggerate the appearance of subsequent declines during the tryptophan period and consequently

Figure 4-4

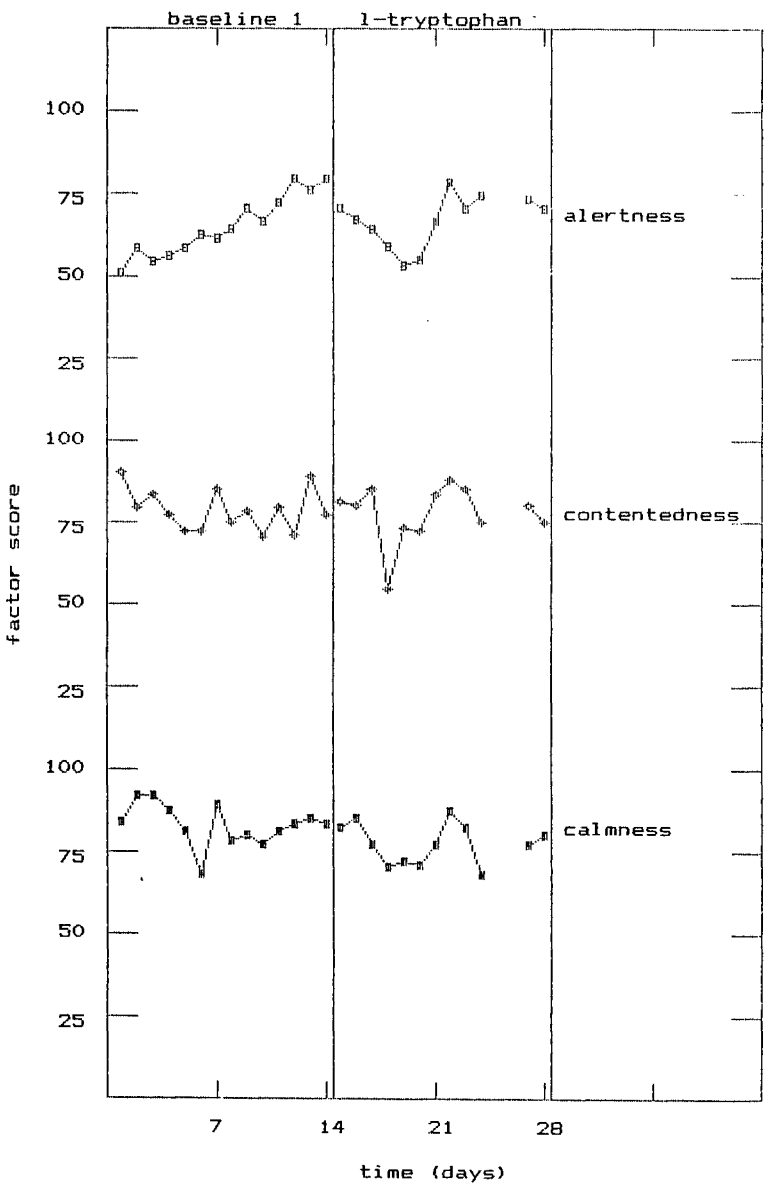
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 04



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 04



detract from the importance of this observation.

Autocorrelation estimates

Table 4-4-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=14)		
	r1	r2	r3	r1	r2	r3
alertness						
morning	.60**	.41*	.37*	.26	.26	-.15
evening	.71**	.59*	.36*	.64**	.18	-.17
cont...ss						
morning	.13	-.31	-.30	-.28	.28	-.24
evening	-.21	.22	-.34*	.06	.02	-.40
calmness						
morning	-.32	-.10	-.01	-.20	.17	-.11
evening	.14	.08	-.21	.27	-.45	-.34

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Table 4-4-4 t test values for mean differences between baseline 1 and tryptophan

	base1 - tryp		
	alertness	contentedness	calmness
morning	-2.04 ns	~ 0.42 ns	0.80 ns
evening	-0.56 ns	0.26 ns	2.25 *

* exceeds critical value for the .05 level of significance

+ sig. t values affected by sig. levels of autocorrelation

- indicates the first mean of the pair is the lowest

Comment on t test results

As is evident from Table 4-4-4, significant differences between baseline and tryptophan periods were limited to the evening series for the calmness dimension. This calculation was free from autocorrelation bias.

C statistic results

Table 4-4-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	3.16 **	~ 0.56 ns
cont...ss	1.02 ns	-0.61 ns
calmness	-1.18 ns	-0.40 ns
evening		
alertness	3.57 **	~ 1.84 ns
cont...ss	-0.31 ns	0.08 ns
calmness	0.57 ns	1.85 ns

** exceeds the critical value for the .01 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see Chapter III for explanation)

Comment on C statistic results

Tryptophan phases did not exhibit any significant departures in trend from baseline on any dimension (Table 4-4-5).

(c) Hours of sleep

Table 4-4-6 Autocorrelation estimates: rk (k=n/4) values

baseline (n=14)			tryptophan (n=14)		
r1	r2	r3	r1	r2	r3
-.21	.03	-.19	-.30	-.20	-.10

None of the above estimates proved significant

t test value results for hours of sleep

base1 - tryp
-1.19 ns

Comment on hours of sleep

There was no significant difference between mean hours of sleep for the baseline and tryptophan periods.

(d) Side effects

Side effects noted by this subject included two experiences of nausea during the baseline phase. During the tryptophan phase, increased appetite was reported on 5 occasions, nausea on 4 occasions, blurred vision twice and dry mouth twice. Thus, there is evidence in this subject of an increase in side effect severity associated with the tryptophan phase.

(5) Summary and Conclusions

Given that the present subject was not considered to be depressed or anxious attention was focused on general mood altering effects. Although visual analysis indicated some decline on the mood dimensions in the first few days of tryptophan ingestion, the increasing trend during the baseline phase probably exaggerated the effects. No changes with respect to side effects or unusual happenings coincided with this early part of the tryptophan phase. The brevity of the series and the absence of placebo phases for comparison limits confidence in the evaluation of tryptophan effects for this subject. On the basis of the available evidence it was concluded that tryptophan administration was not associated with any consistent mood altering effects. The most notable effects associated with tryptophan intake related to the increase in reported side effects, particularly 'increased appetite'.

4.2.5 Subject 05

(1) Demographic variables

age(yrs): 25 sex: female height(cms):168
weight(kgs):57.20
(within desirable weight range)

motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The present subject was classified as 'non depressed' on the basis of low SDS scores throughout the trial i.e. all were below the mean with respect to Knight et al.'s (1983) norms, (see Table 4-5-1), in keeping with the motivation for participation.

(b) Anxiety status

The Trait anxiety score for this subject (39) was close to the approriate mean for a normal population while the initial State score (25) was relatively low (Knight et al., 1983). Consequently, this subject was considered to be relatively free from anxiety symptoms.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	14days	7days	14days	7days

(c) Extra details

As is evident from the graphed mood data (Figures 4-5-1 and 4-5-2), scale completion was missed by this subject on several occasions throughout both series. Otherwise completion time was regular and tablet consumption was not forgotton on any occasion.

(4) Results and analysis

(a) Weekly scores

Table 4-5-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56
scale									
zung	27	25	23	24	23	-	29	24	-
state	25	37	33	37	40	-	39	34	-
HSCL	76	74	73	68	64	-	63	71	-

Table 4-5-2 HSCL factor scores

	baseline 1			tryptophan		wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56
factor									
1	1.12	1.30	1.16	1.00	1.00	-	1.00	1.09	-
2	1.77	1.35	1.35	1.23	1.24	-	1.23	1.47	-
3	1.29	1.29	1.29	1.29	1.16	-	1.12	1.46	-
4	1.16	1.36	1.19	1.26	1.08	-	1.08	1.18	-
5	1.00	1.15	1.15	1.15	1.15	-	1.00	1.00	-

Comment on weekly scale scores

Low scores were maintained throughout the trial on all the weekly scales and HSCL factor scores were close to the normal sample (Table 3-4) according to Derogatis et al., (1974).

(b) Mood factors

Visual analysis of graphed data

As is evident from graphed data for both morning and evening series (Figures 4-5-1 and 4-5-2), a relatively high level of missing data was accrued by this subject. During the evening series there was a slight but consistent drop in contentedness level for the tryptophan and washout periods relative to the baseline phase. Otherwise, there was considered

Figure 4-5-1
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 05

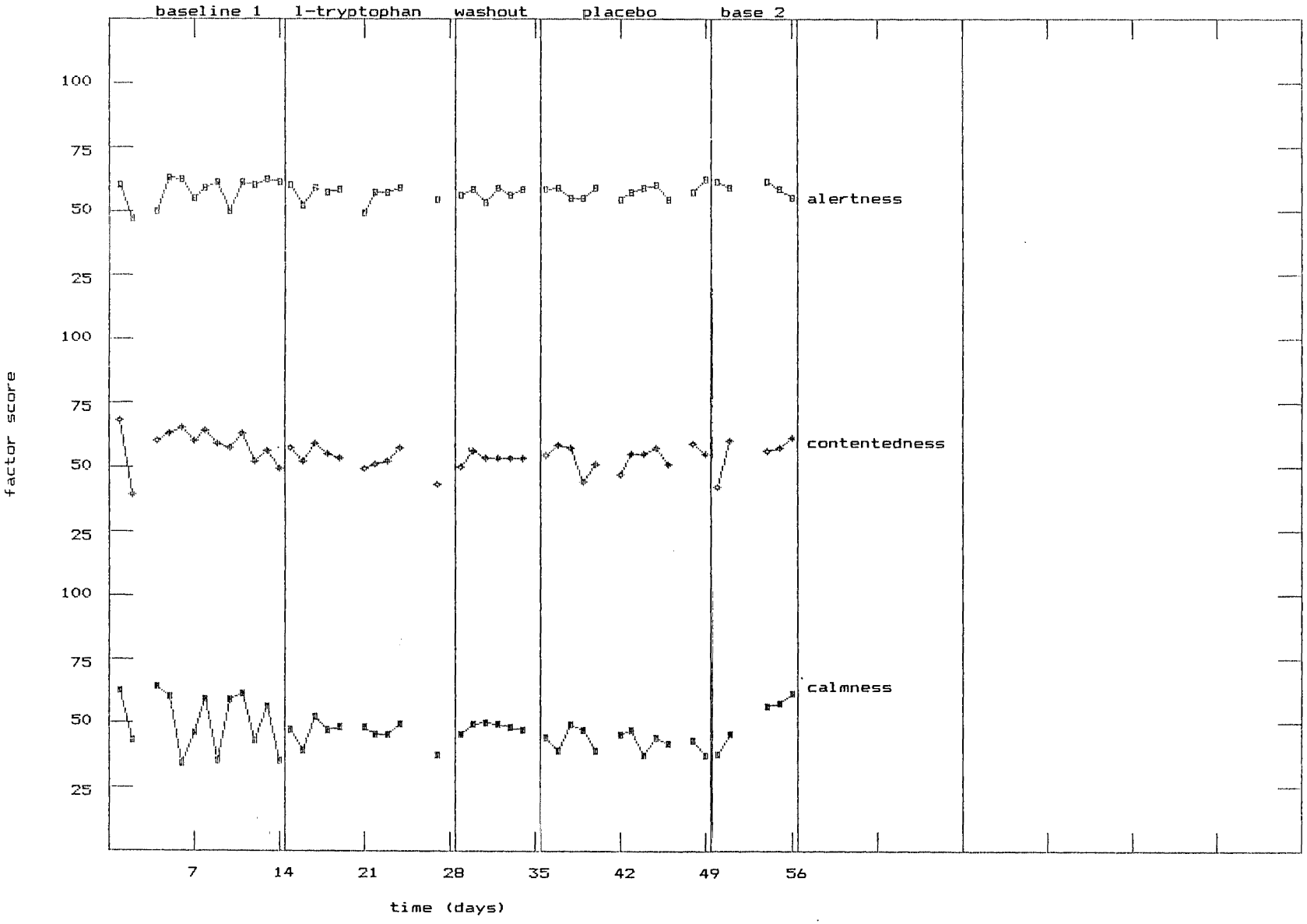
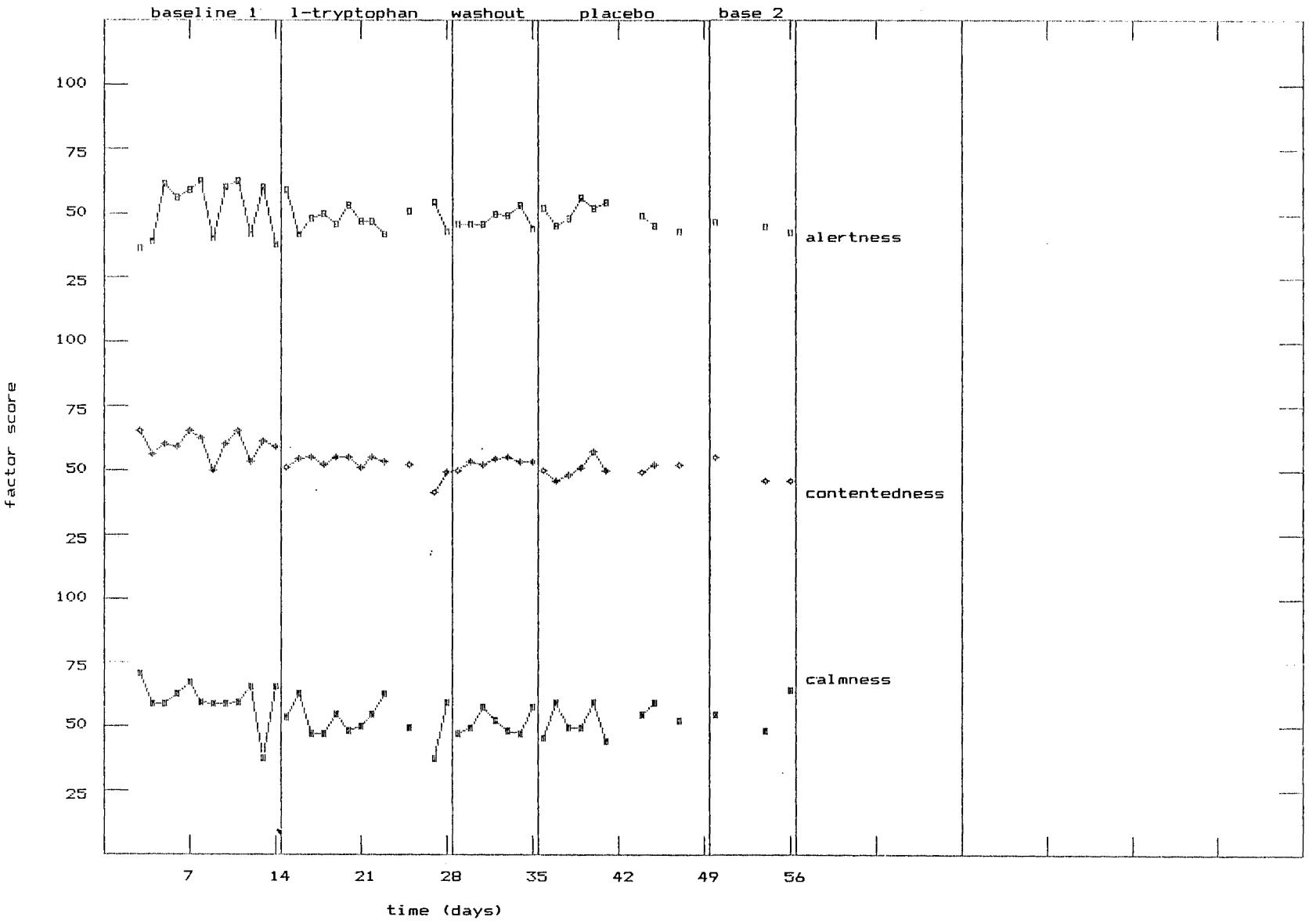


Figure 4-5-2

FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 05



to be a lack of sufficiently dramatic or meaningful changes between or within phases for either series.

Autocorrelation estimates

Table 4-5-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1			tryptophan			placebo		
	r1	r2	r3	r1	r2	r3	r1	r2	r3
alertness									
morning	.02	-.34	.05	-.42	.02	-	-.15	-.42	.23
evening	-.02	-.08	.05	-.37	-.18	.09	.26	-.15	-
cont...ss									
morning	-.22	.06	-.09	-.16	.10	-	.04	.07	-.30
evening	-.33	-.36	.24	.25	.01	-.05	.17	-.40	-
calmness									
morning	-.36	-.15	.36*	-.36	.09	-	-.28	-.21	.36
evening	-.33	-.01	.03	-.18	-.45	.10	-.50*	-.13	-

* exceeds the critical value for the .05 level of significance

t test results

Table 4-5-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	0.80 ns	~ 0.21 ns	-0.95 ns
evening	~ 0.49 ns	~ 0.28 ns	3.75 **
contentedness			
morning	1.90 ns	~ 1.78 ns	-0.40 ns
evening	4.31 **	4.98 **	0.85 ns
calmness			
morning	~ 1.39 ns	~ 2.30 *	1.61 ns
evening	2.49 *	2.29 *+	-0.13 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

+ sig. t values affected by sig. levels of autocorrelation

- indicates the first mean of the pair is the lowest

Comment on t test results

For the alertness dimension, the mean for the tryptophan phase was found to be significantly higher than placebo, however there was no significant elevation with respect to the baseline phase. For the contentedness dimension tryptophan and placebo means were significantly lower than baseline during the evening but were not different from each other. Finally, for the calmness dimension, the mean for tryptophan in the morning series was signficantly below the mean for the baseline period. The placebo mean was also found to be significantly below baseline in morning and evening series. The significance level associated with the evening difference may have been underestimated due to the presence of significant levels of negative autocorrelation in the placebo phase for this series.

C statistic results

Table 4-5-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	0.20 ns	-0.06 ns
cont...ss	-0.36 ns	0.40 ns
calmness	-0.93 ns	-0.90 ns
evening		
alertness	0.73 ns	0.24 ns
cont...ss	-1.04 ns	2.00 *
calmness	-0.90 ns	0.13 ns

* exceeds the critical value for the .05 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see section Chapter III for explanation)

Comment on C statistic results

The only signifcant result, indicated from Table 4-5-5, was for a departure of the tryptophan phase relative to baseline for the contentedness dimension during the evening series.

(c) Hours of sleep

Table 4-5-6 Autocorrelation estimates: rk (k=n/4) values

baseline1			tryptophan		placebo		
r1	r2	r3	r1	r2	r1	r2	r3
-.01	-.06	-.23	-.25	-.20	-.22	-.21	.01

None of the above estimates proved significant

t test value results for hours of sleep

base1 - tryp	base1 - tryp	tryp - plac
~ 1.39 ns	~-0.59 ns	~-1.56 ns

Comment on hours of sleep

As evident from the above t test results, there was no significant difference in the mean hours of sleep between baseline 1, tryptophan or placebo phases.

(e) Side effects

No side effects were checked by this subject throughout the trial period.

(5) Summary and Conclusions

Due to the absence of depressive or anxious symptoms in this subject evaluation was focused on general mood alteration. As indicated from visual analysis, evaluation was hindered due to the high level of missing data. However the indication of a reduction in level for contentedness during the tryptophan phase (relative to baseline) in the evening series was supported by statisitical outcomes. That is, t test results indicated a significantly lower mean for the tryptophan phase relative to baseline and C statistc results indicated a significant departure in trend between the two phases. However, t test comparisons also indicated a significant drop for the placebo relative to baseline phase on this dimension in the evening. Finally, although consistency between visual and statistical

analysis was demonstrated in this case, the change was visually slight and consequently not considered to be of particular psychological relevance. No other changes such as increased side effects of changes in total sleep time were associated with the tryptophan phase for this subject.

The suggestion of increased alertness for the tryptophan phase relative to placebo in the morning was not considered particularly meaningful. There was no indication of increased tryptophan alertness relative to baseline for this series. The significant mean reduction in calmness for placebo and tryptophan relative to baseline during the morning was not considered particularly important in light of the high variability apparent in the baseline phase. Similarly, the statistically significant evening calmness reduction for placebo relative to baseline could not be supported by visual analysis. Thus, tryptophan administration (3gms/day) in this subject did not relate to any consistent or meaningful changes in psychological state, including side effects and total sleep time.

4.2.6 Subject 06

(1) demographic variables

age(yrs): 24 sex: male height(cms):183
weight(kgs):71.00
(within desirable weight range)

l-tryptophan experience: - not consumed prior to this project

motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial SDS total score for this subject was close to the normal mean with respect to Knight et al.'s (1983) norms (see table 1). A single subsequent score, during the remaining trial period exceeded one standard deviation above this mean.

Consequently, this subject was assigned a 'non depressed' status which was in keeping with the general interest motivation for participation.

(b) Anxiety status

The Trait anxiety score for this subject was close to the appropriate normal mean (Knight et al., 1983). Initial and subsequent State scores were generally close to or below the appropriate mean. Thus, the present subject was considered to be relatively free from anxiety symptoms.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	14days	7days	14days	7days

(c) Extra details

Scale completion time was regular for this subject. Although some daily scales were missed, the tryptophan and placebo periods were essentially complete. No tablets were forgotton during tryptophan and placebo phases.

4.2.6.4 Results and analysis

(a) Weekly scores

Table 4-6-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56
scale									
zung	30	39	34	32	27	35	35	32	32
state	27	26	32	32	29	27	28	29	24
HSCL	66	68	64	70	69	68	68	63	66

Table 4-6-2 HSCL factor scores

	baseline 1			tryptophan		wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56
factor									
1	1.18	1.08	1.08	1.33	1.15	1.18	1.17	1.00	1.00
2	1.00	1.23	1.23	1.12	1.12	1.34	1.22	1.00	1.35
3	1.00	1.10	1.00	1.00	1.00	1.00	1.00	1.00	1.00
4	1.35	1.37	1.08	1.27	1.25	1.17	1.26	1.27	1.10
5	1.00	1.00	1.00	1.42	1.15	1.16	1.16	1.00	1.16

Comment on weekly scale scores

Total scores for all weekly scales remained consistently low throughout the trial period, reinforcing the non depressed and non anxious status of this subject. There was some indication from the HSCL factor scores (Table 4-6-2), of a rise in the somatization and anxiety dimensions during the first week of tryptophan ingestion. HSCL factor scores were close to normal sample means (Table 3-4) according to Derrogatis et al. (1974).

(b) Mood factors

Visual analysis of graphed data

No obvious patterns emerged from visual analysis of the graphed moodscale data (Figures 4-6-1 and 4-6-2) for this subject, either between or within phases. No clear differences were apparent between morning and evening plots.

Figure 4-6-1

FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 06

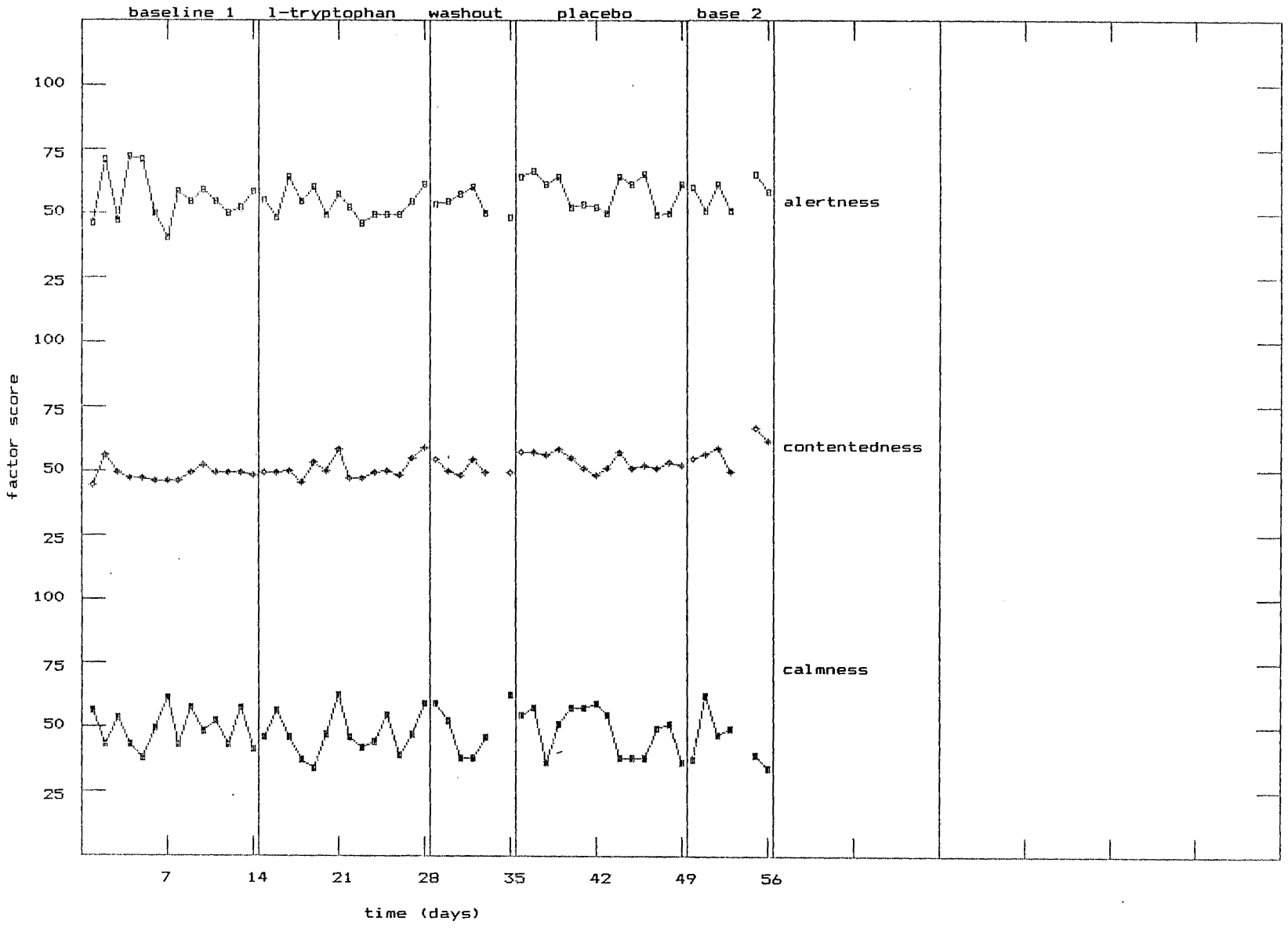
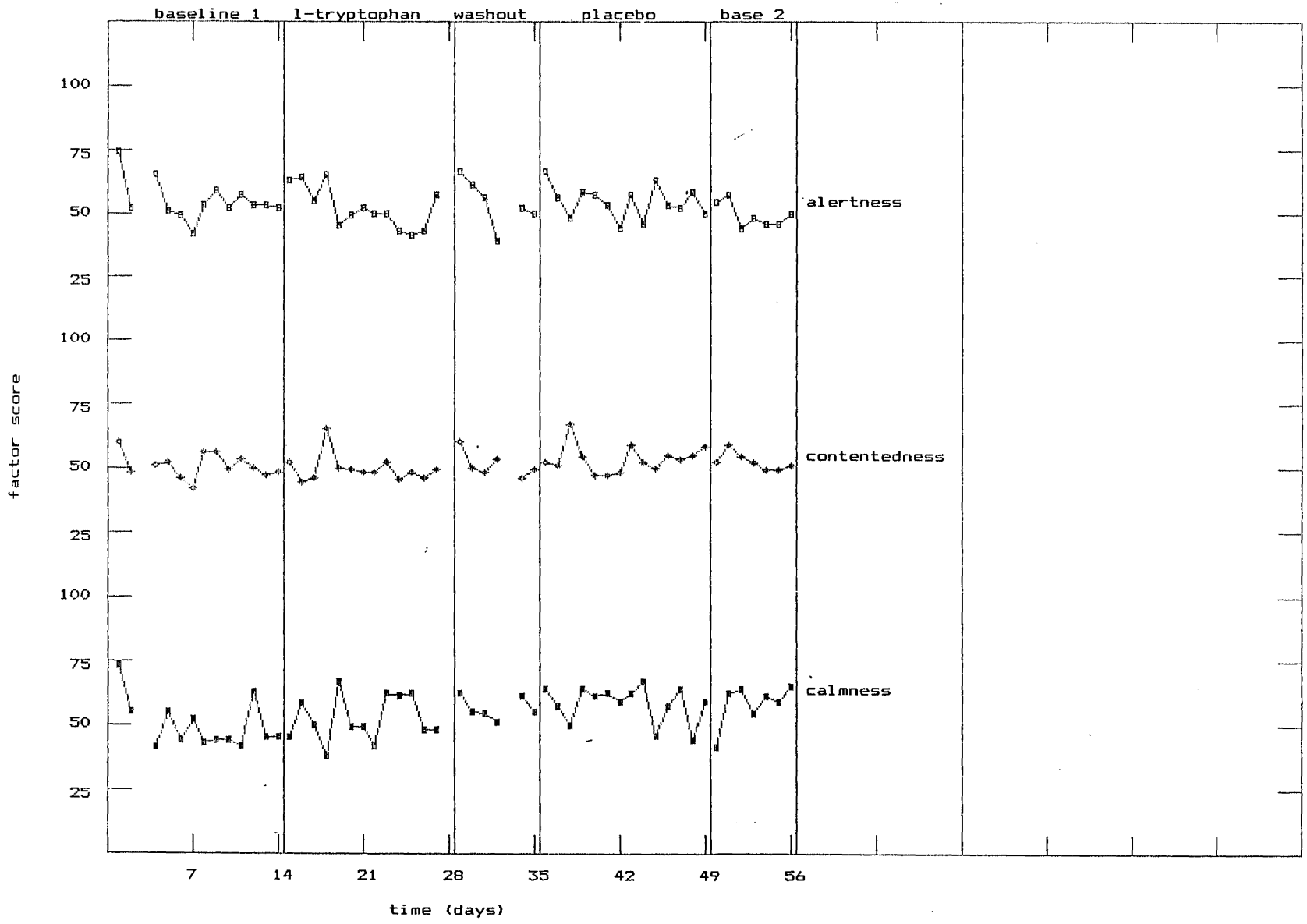


Figure 4-6-2
FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 06



Autocorrelation estimates

Table 4-6-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1			tryptophan			placebo		
	r1	r2	r3	r1	r2	r3	r1	r2	r3
alertness									
morning	-.16	-.11	-.12	-.06	.27	-.18	.25	-.06	-.32
evening	-.03	.23	-.25	.38*	.25	.08	-.30	-.03	-.00
cont...ss									
morning	-.08	-.08	-.08	.04	-.03	-.24	.44	.06	-.08
evening	-.04	-.31	.10	-.12	-.26	.05	.05	-.33	-.19
calmness									
morning	-.42	.14	-.14	.06	-.52*	-.20	.27	-.09	-.10
evening	-.05	-.10	.09	-.20	-.18	-.16	-.27	-.22	.40

* exceeds the critical value for the .05 level of significance

t test results

Table 4-6-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	~ 0.83 ns	-0.68 ns	-2.04 ns
evening	0.85 ns	0.15 ns	-0.81 ns
contentedness			
morning	-1.68 ns	-4.49 **	-2.05 *
evening	0.62 ns	-1.43 ns	-1.97 ns
calmness			
morning	0.61 ns	0.21 ns	-0.35 ns
evening	-0.70 ns	-2.68 *	-1.98 ns

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

- indicates the first mean of the pair is the lowest

Comment on t test results

Significant mean phase differences were limited to contentedness and calmness dimensions. As indicated in Table 4-

6-4, the mean for the tryptophan morning phase on contentedness was significantly lower than the placebo period. However, the baseline phase was also significantly lower than placebo in this series. The other finding was for a significantly higher mean on calmness during the tryptophan relative to baseline period in the evening.

C statistic results

Table 4-6-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	-0.49 ns	-0.34 ns
cont...ss	0.01 ns	1.18 ns
calmness	-1.37 ns	-0.34 ns
evening		
alertness	0.87 ns	1.78 *
cont...ss	-0.02 ns	-0.38 ns
calmness	0.80 ns	0.29 ns

* exceeds the critical value for the .05 level of significance

Comment on C statistic results

There was a significant departure in trend for the evening tryptophan phase relative to baseline on the dimension of alertness.

(c) Hours of sleep

Table 4-6-6 Autocorrelation estimates: rk (k=n/4) values

baseline1			tryptophan			placebo		
r1	r2	r3	r1	r2	r3	r1	r2	r3
.19	-.19	-.30	.07	-.56*	-.13	.20	.01	-.12

* exceeds the critical value for the .05 level of significance

t test value results for hours of sleep

base1 - tryp	base1 - tryp	tryp - plac
-0.78 ns	~ 1.34 ns	1.60 ns

Comment on hours of sleep

No significant differences between baseline, tryptophan or placebo phases were noted for mean hours of sleep.

(d) Side effects

Side effect reports for this subject were low. No effects were noted during the placebo phase. The mean severity of reported effects showed little change between baseline (1.4) and tryptophan (1.0) phases. Similarly, the qualitative structure of most symptoms showed little variation between phases. Two symptoms unique to the tryptophan phase were reported on several occasions during the first week, i.e. stomach cramps and difficulty falling asleep.

(5) Summary and Conclusions

Results from visual and statistical analysis confirmed a lack of general mood altering effects associated with tryptophan administration in this subject. The statistically significant reduction in the mean for the contentedness dimension relative to placebo, in the morning, was not supported by a reduction relative to baseline. The indication of a departure in trend on evening alertness for tryptophan relative to placebo was not considered sufficiently dramatic or meaningful following visual analysis of these periods. The most notable feature for this subject which appeared specifically associated with the tryptophan period was the appearance of stomach cramps and sleeping difficulty in the first week of tryptophan administration.

4.2.7 Subject 07

(1) Demographic variables

age(yrs): 60 sex: female height(cms):164

weight(kgs):69.85

(above desirable weight range)

l-tryptophan experience: - not consumed prior to this project

motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

Initial and subsequent SDS scores for the present subject were close to the mean of the appropriate age and sex category according to Knight et al.'s (1983) norms. On the basis of these ratings and a 'general interest' motivation for participation, the present subject was classified as 'non depressed'.

(b) Anxiety status

With respect to Knight et al.'s (1983) norms this subject exhibited initial Trait (32) and State (28) anxiety scores in keeping with the means for her age category. On this basis the present subject was considered relatively free from significant levels of anxiety.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan
14days	7days

(c) Extra details

The brevity of the trial period in this case was due to the need for this subject to withdraw from the experiment following a sudden requirement to move from her home. Scale completion time was regular, i.e. within a two hour day to day variation, with no missing data accrued. No tryptophan tablets were forgotten during the 7 day phase.

(4) Results and analysis

(a) Weekly scores

Table 4-7-1
Total scores for Zung, State anxiety and HSCL scales

	baseline 1		
day	01	07	14
scale			
zung	34	35	32
state	28	42	36
HSCL	75	84	82

Table 4-7-2
HSCL factor scores

	baseline 1		
day	01	07	14
factor			
1	1.00	1.28	1.18
2	1.51	1.60	1.47
3	1.16	1.34	1.34
4	1.44	1.45	1.45
5	1.43	2.02	2.02

Comment on weekly scale scores

As is evident from Tables 4-7-1 and 4-7-2, weekly scale ratings for the initial baseline phase remained relatively low on all scales, except for the elevation in the State score on day seven. This rating coincided with the day the subject was informed of the requirement to vacate her home. HSCL factor scores were close to means for the normal sample (Table 3-4). A rise in the HSCL factor 5 was apparent on day seven and 14 relative to the initial value. Factor 5 represents the dimension labelled 'anxiety' for this scale. This finding tends to be in agreement with the increased State anxiety scores on days seven and 14 relative to the initial rating.

(b) Mood factors

Visual analysis of graphed data

The brevity of both series for this subject (Figure 4-7) imposed extreme limitations on establishing any confident interpretations of the graphed data. No meaningful changes were apparent between the two phases for this subject. Comparison of the morning and evening series indicated close similarity in the day to day fluctuations for the contentedness and calmness dimensions. However, the evening series was noticably depressed on the alertness dimension relative to the morning series.

Autocorrelation estimates

Table 4-7-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1 (n=13)			tryptophan (n=7)
	r1	r2	r3	r1
alertness				
morning	.01	.17	-.12	-.30
evening	.25	-.11	-.12	-.52*
cont...ss				
morning	.05	.17	-.34	.09
evening	.13	.03	-.05	-.33
calmness				
morning	.32	-.18	.00	-.33
evening	.36*	-.05	-.29	.12

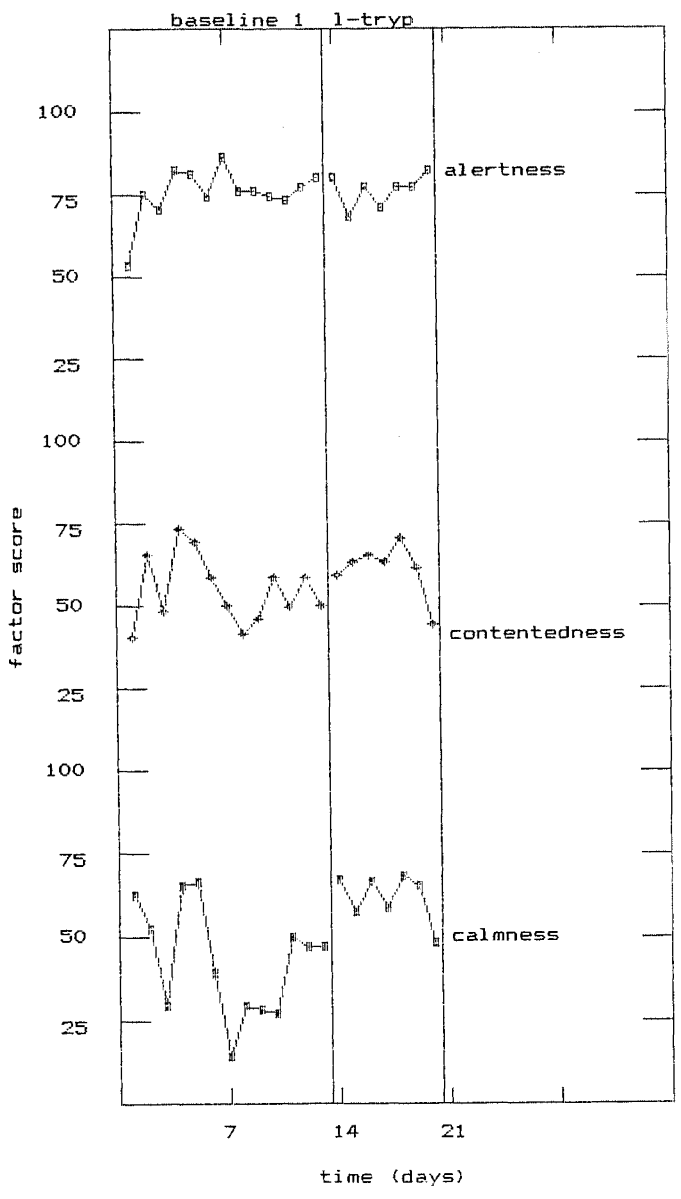
* exceeds the critical value for the .05 level of significance

(c) Hours of sleep

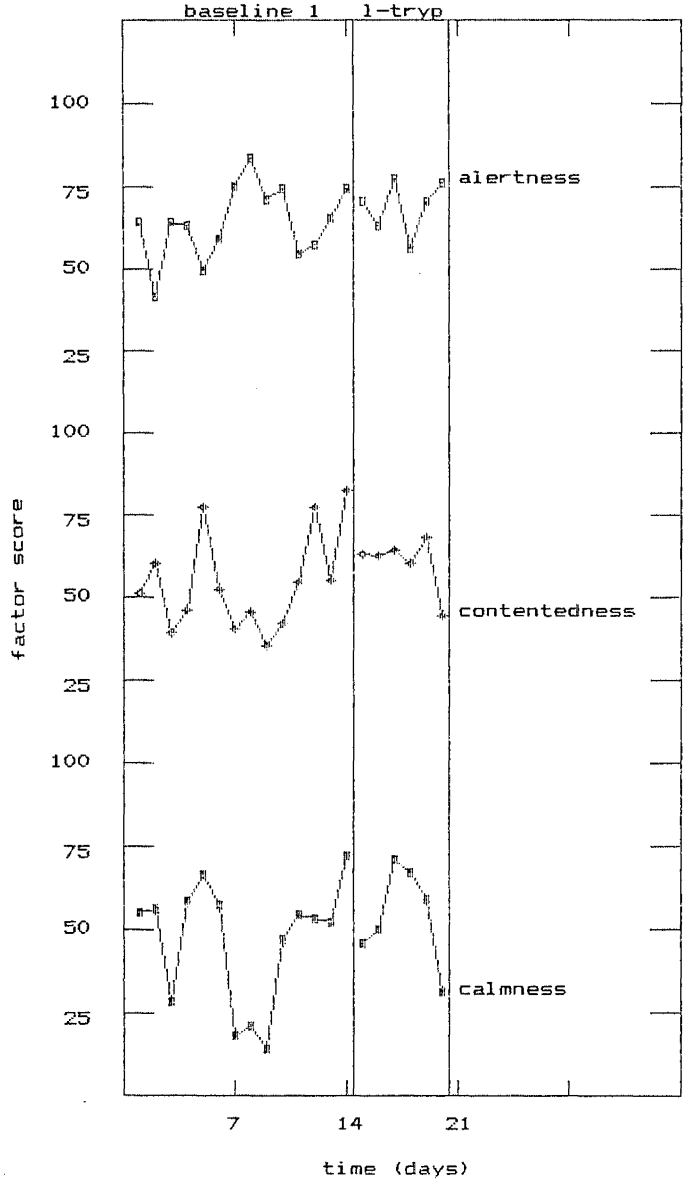
The information relating to hours of sleep was insufficient to allow for valid statistical analysis between phases i.e. only four ratings were obtained for the tryptophan phase. The means for the baseline 1 and tryptophan phases were 5.1 and 6.25 respectively, indicating no marked change for the brief tryptophan period.

Figure 4-7

FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 07



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 07



(d) Side effects

The incidence of reported side effects was low for this subject and limited to one symptom in both phases. That is, headaches were recorded twice in both baseline 1 and tryptophan phases.

(5) Summary and Conclusions

The value of including the data for this subject is obviously limited. However, it was not considered justifiable to ignore subjects on the basis of shorter than desirable data series. Although the present subject only completed one week on tryptophan it may have been sufficient to establish the presence of undesirable side effects. That is, other subjects with side effect elevation during the tryptophan phase generally exhibited such increases by the first week of tryptophan ingestion. In this regard, the present subject did not demonstrate any marked elevation in side effects during the tryptophan relative to baseline phase. Visual analysis failed to indicate any relevant changes in the mood dimensions between baseline and tryptophan periods. It is possible that the presence of autocorrelation in parts of the mood series may have misled visual evaluation in this case. Jones et al. (1977) have indicated that autocorrelation may corrupt the process of visual analysis. However, the brevity of the tryptophan phase in this case would have required particularly dramatic and consistent effects before much confidence could be attached to between or within phase changes.

4.2.8 Subject 08

(1) Demographic variables

age(yrs): 19 sex: female height(cms):152
weight(kgs):59.00
(within desirable weight range)

chemical contraceptives?: yes
PMT?: yes

tryptophan experience: not consumed prior to this project
motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

Initial and subsequent SDS total scores for this subject were below the appropriate mean according to Knight et al.'s (1983) norms. On this basis and the 'general interest' motivation for participation, the present subject was classed as 'non depressed'.

(b) Anxiety status

With respect to Knight et al.'s (1983) norms this subject exhibited a low Trait anxiety score and all State scores were below the corresponding mean, indicating freedom from significant levels of anxiolytic symptoms.

(1) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout
14days	14days	7 days

(c) Extra details

Scale completion time was regular with missing data limited to one evening baseline rating. No tablets were forgotten during the tryptophan phase.

(4) Results and analysis

(a) Weekly scores

Table 4-8-1
Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan	
day	01	07	14	21	28
scale					
zung	32	34	31	28	26
state	33	33	32	35	29
HSCL	67	79	64	76	67

Table 4-8-2
HSCL factor scores

	baseline 1			tryptophan	
day	01	07	14	21	28
factor					
1	1.07	1.15	1.00	1.18	1.34
2	1.00	1.12	1.00	1.12	1.00
3	1.52	1.46	1.30	1.73	1.16
4	1.10	1.62	1.09	1.36	1.08
5	1.15	1.15	1.15	1.15	1.16

Comment on weekly scale scores

Low total scores on the weekly scales were maintained throughout the trial period and no dramatic changes were noted between the two phases completed. Similarly, no consistent differences between phases were noted on the basis of HSCL factor scores. HSCL factor scores were close to the means for a normal sample (Table 3-4).

(b) Mood factors

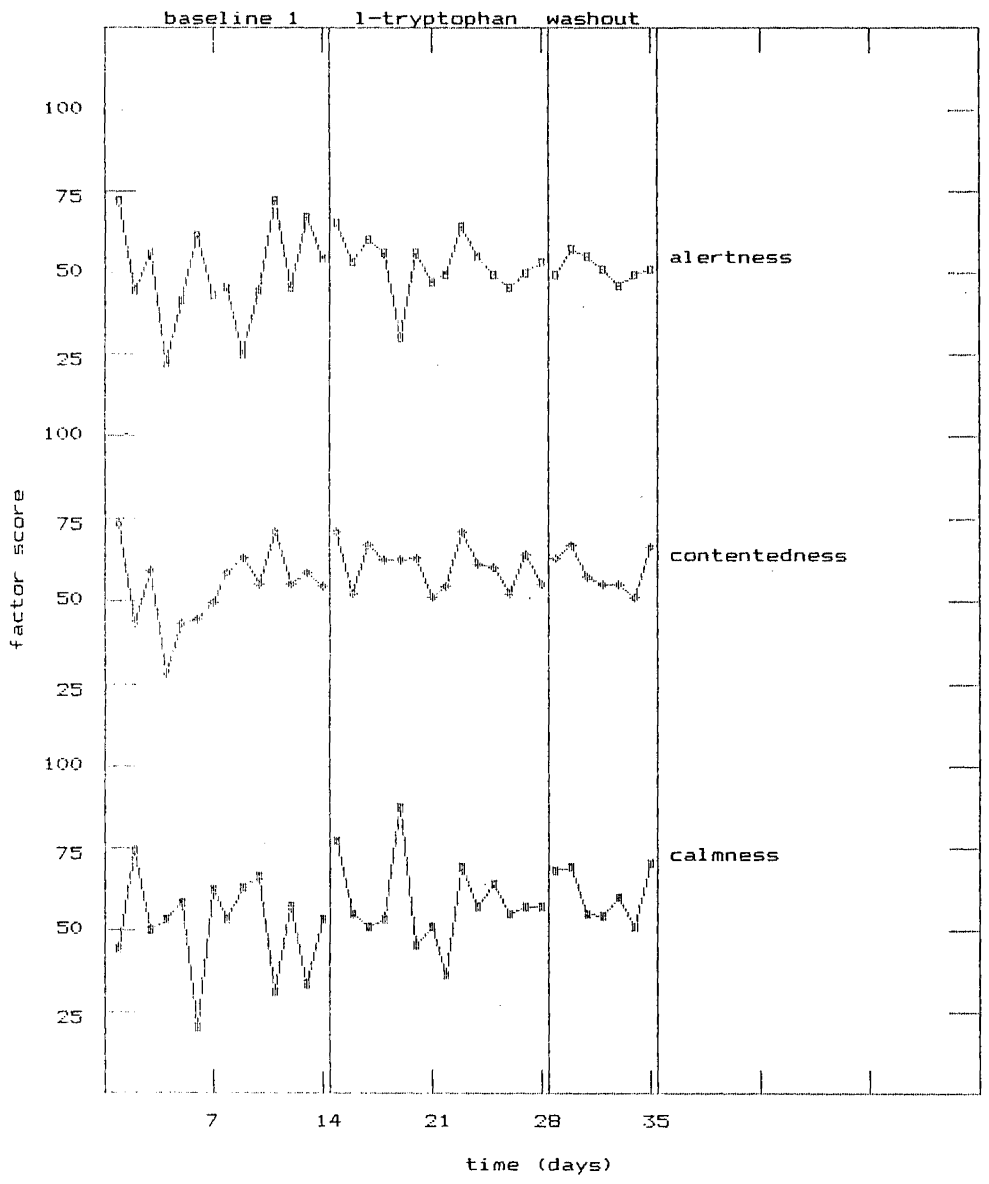
Visual analysis of graphed data

Graphed mood data for both morning and evening series (Figure 4-8) exhibited high day to day variability across all phases. There was some indication of a reduction in alertness for the tryptophan relative to baseline phase in the evening series as well as a slight increase in calmness. However, the variability in the series reduced confidence in this finding.

Figure 4-8

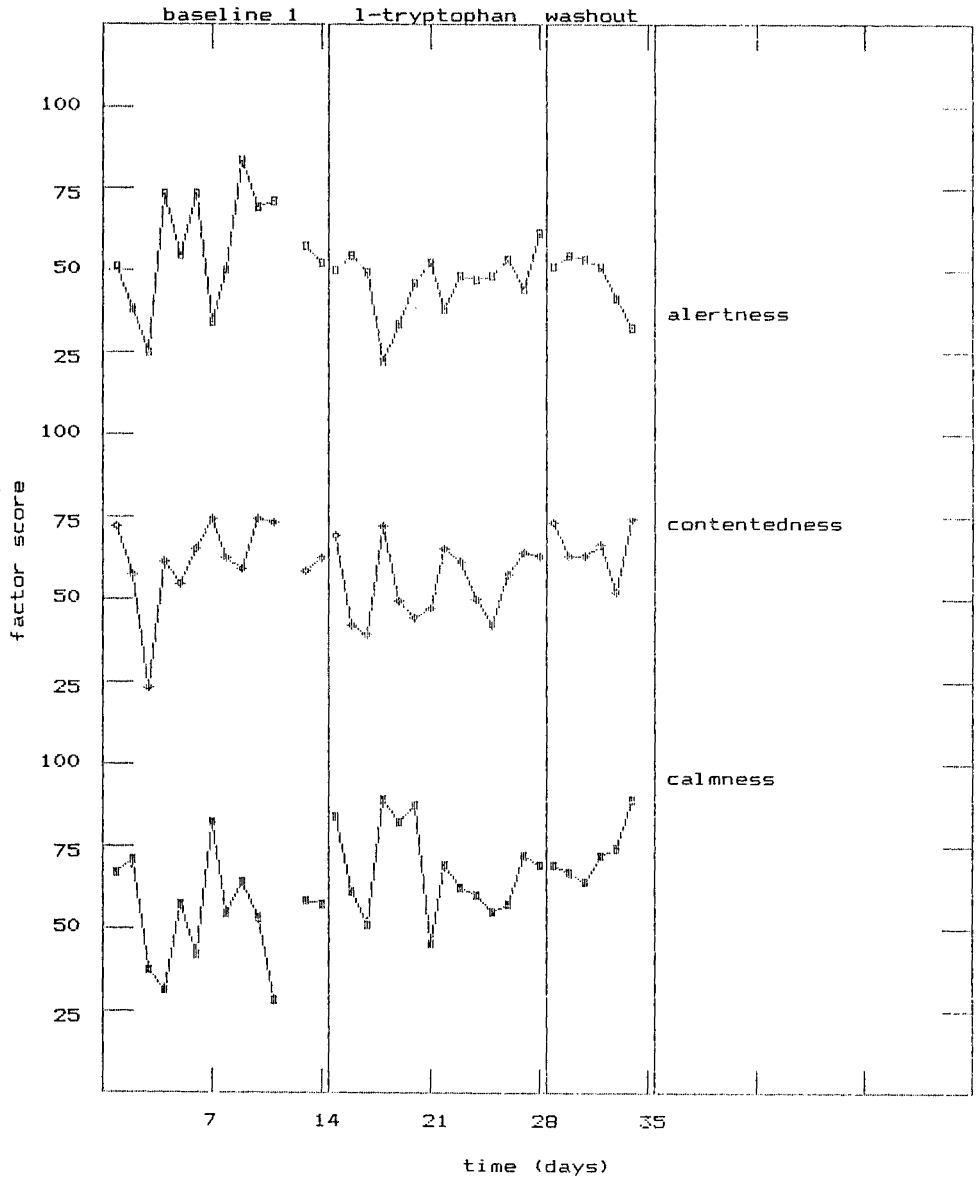
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 08



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 08



Autocorrelation estimates

Table 4-8-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=14)		
	r1	r2	r3	r1	r2	r3
alertness						
morning	-.08	-.01	-.17	-.10	-.08	.06
evening	.06	-.05	-.25	.17	-.15	-.17
cont...ss						
morning	.06	.42*	-.19	-.34	-.05	-.11
evening	.11	-.14	.03	-.08	-.56*	-.00
calmness						
morning	-.38	.13	-.09	-.25	-.07	-.46
evening	-.06	-.12	-.26	-.01	-.14	-.19

* exceeds the critical value for the .05 level of significance

t test results

Table 4-8-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp
alertness	
morning	~-0.62 ns
evening	~ 1.86 ns
contentedness	
morning	~-1.80 ns
evening	1.38 ns
calmness	
morning	-1.32 ns
evening	-2.34 *

* exceeds critical value for the .05 level of significance

- indicates the first mean of the pair is the lowest

~ phase variances unequal,t-test approximation used(see Chapter III)

Comment on t test results

There was a significantly greater mean for tryptophan relative to baseline in the evening for the calmness dimension.

C statistic results

Table 4-8-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	0.05 ns	0.02 ns
cont...ss	0.65 ns	0.65 ns
calmness	-1.47 ns	-1.14 ns
evening		
alertness	0.25 ns	0.27 ns
cont...ss	0.54 ns	0.76 ns
calmness	-0.14 ns	0.69 ns

Comment on C statistic results

As indicated from Table 4-8-5, no significant changes in trend between baseline and tryptophan periods were detected following application of the C statistic.

(c) Hours of sleep

Table 4-8-6 Autocorrelation estimates: rk (k=n/4) values

baseline (n=14)			tryptophan (n=14)		
r1	r2	r3	r1	r2	r3
-.02	-.04	-.44	.08	-.31	.29

None of the above estimates proved significant

t test value results for hours of sleep

base1 - tryp
0.55 ns

Comment on hours of sleep

There was no significant change noted between trptophan and baseline periods in mean hours of sleep.

(d) Side effects

The severity of side effects reported by this subject was low across all phases. There was little change in means between baseline (0.5) and tryptophan (0.64) periods. The only symptoms unique to the tryptophan phase included: dry mouth, increased appetite and dizziness. However, such effects were only noted on one occasion.

(e) Premenstrual tension

The present subject responded positively to suffering from premenstrual tension. The only onset of menstrual bleeding was noted on the 6th day of the tryptophan phase. There was a slight suggestion of increased variability in mood ratings for the premenstrual phase relative to the latter parts of the series on some dimensions. However, the visual impression was slight and was not considered to threaten the validity of the phase changes discerned.

(5) Summary and Conclusions

The absence of a placebo phase for the present subject imposed limitations on the evaluation. However, there were no dramatic or consistent changes noted with respect to mood ratings between baseline and tryptophan phases. The visual indication of an increase in calmness for the evening tryptophan phase relative to baseline was supported by the statistical finding of an increased mean in this direction. The visual impression of a slight reduction in alertness for the evening tryptophan phase relative to baseline was not, however, supported statistically and the change was not considered of sufficient magnitude to be of psychological relevance. Thus, there was a lack of general mood alteration associated with tryptophan intake of 3gms/day in this subject. In addition, no significant or meaningful changes with respect to mean hours of sleep or side effect severity were detected.

4.2.9 Subject 09

(1) Demographic variables

age(yrs): 19 sex: male height(cms):183
weight(kgs):70.00
(within desirable weight range)

tryptophan experience: - not consumed prior to this project
motivation for participation: - depression

(2) Psychological variables

(a) Depression status

Initial and subsequent SDS scores (with one exception) for this subject were within one standard deviation above the appropriate mean with respect to Knight et al.'s (1983) norms. However, this subject clearly indicated 'depression' as his motivation for participation. The one elevated total score of 40 just reaches inclusion in Zung's (1972) category for "mild to moderate" depression. On the basis of the motivation for participation and the fact that this subject had been taking conventional antidepressants prior to the present experiment led to consideration of antidepressant effects for this subject.

(b) Anxiety status

The initial Trait anxiety score for this subject of 52 was in excess of 2 standard deviations above the mean according to Knight et al.'s (1983) norms. Baseline State scores exceeded one standard deviation from the appropriate mean. As is evident from Table 4-9-1, later State scores were extremely elevated e.g. in excess of 5 standard deviations above the normative mean (Knight et al., 1983). Consequently, the present subject was considered to be experiencing considerable levels of anxiety relative to the normal population and attempts were made to evaluate the anti-anxiety potential of tryptophan administration in this subject.

(3) Experimental variables

(a) Dose level(gms/day): 6

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	28days	7days	14days	7days

(c) Extra details

Scale completion time was regular. Moodscale scale completion was missed occasionally and was not considered to significantly limit data interpretation. No tablets were forgotton by this subject during tryptophan or placebo phases.

(4) Results and analysis

(a) Weekly scores

Table 4-9-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan				wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56	63	70
scale											
zung	-	37	32	36	33	38	34	40	39	41	35
state	-	40	45	30	57	34	39	61	71	53	33
HSCL	-	92	105	103	98	103	105	124	124	128	96

Table 4-9-2 HSCL factor scores

	baseline 1			tryptophan				wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56	63	70
factor											
1	-	1.08	1.19	1.19	1.17	1.23	1.43	1.64	1.66	1.73	1.55
2	-	1.88	2.10	2.36	1.75	2.22	2.12	2.51	2.52	2.47	1.88
3	-	1.85	1.85	2.01	2.03	2.27	2.11	2.58	2.47	2.29	1.73
4	-	2.09	2.28	2.09	2.18	1.82	1.79	2.27	2.35	2.46	1.72
5	-	1.43	1.73	1.43	1.28	1.47	1.47	2.02	2.18	2.18	1.31

Comment on weekly scale scores

SDS total scores were maintained at a constant average level (according to Knight et al.'s (1983) norms) throughout the trial. Some increase in State and HSCL total scores was evident through the washout and placebo phases. Examination of the HSCL factor scores indicated most of the elevation in total scores was attributable to increases on the anxiety dimensions followed by depression. Most HSCL factor scores were close the the means for a depressed sample (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

As is evident from Figures 4-9-1 and 4-9-2, both morning and evening series for this subject exhibited high levels of day to day variability. No consistent trends or other alterations between phases were apparent. On day 16 of the tryptophan phase (morning series), the subject reported an inability to sleep due to environmental noise on the previous night. The mood dimension scores for this day exhibited a decline. However, the drop was not outstanding relative to adjacent days for each dimension.

Autocorrelation estimates

Table 4-9-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=27)			
	r1	r2	r3	r1	r2	r3	r4
alertness							
morning	.26	-.22	-.56*	-.02	-.34	-.28	.35*
evening	.22	.30	-.27	.19	.12	-.17	-.17
cont...ss							
morning	.30	-.22	-.48*	.07	-.12	-.16	.04
evening	.07	.001	-.12	.08	-.22	.17	.10
calmness							
morning	.40	.14	.22	.08	-.09	-.11	.15
evening	.09	.07	.32	.12	-.19	.02	-.08

Figure 4-9-1
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 09

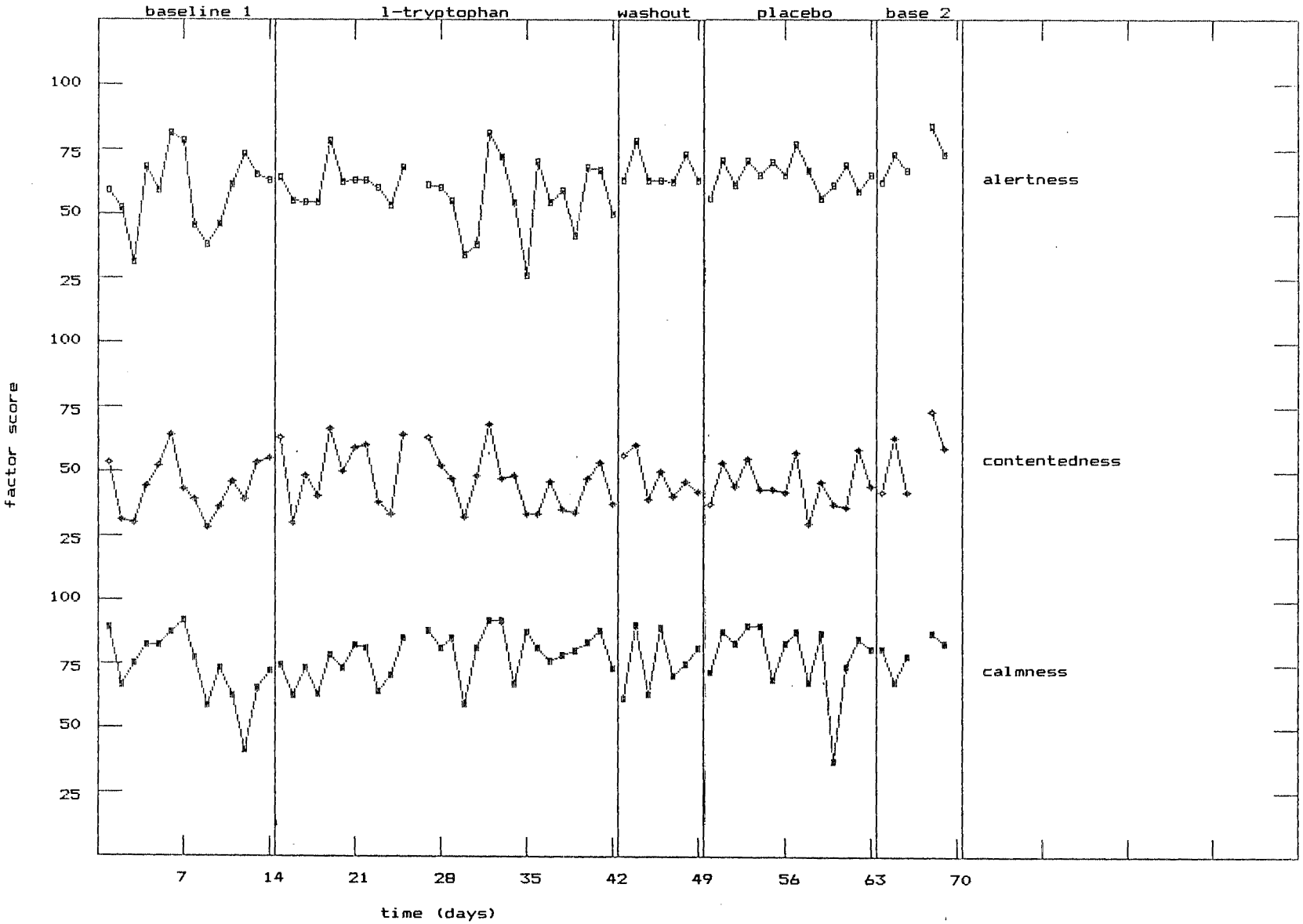


Figure 4-9-2
FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 09

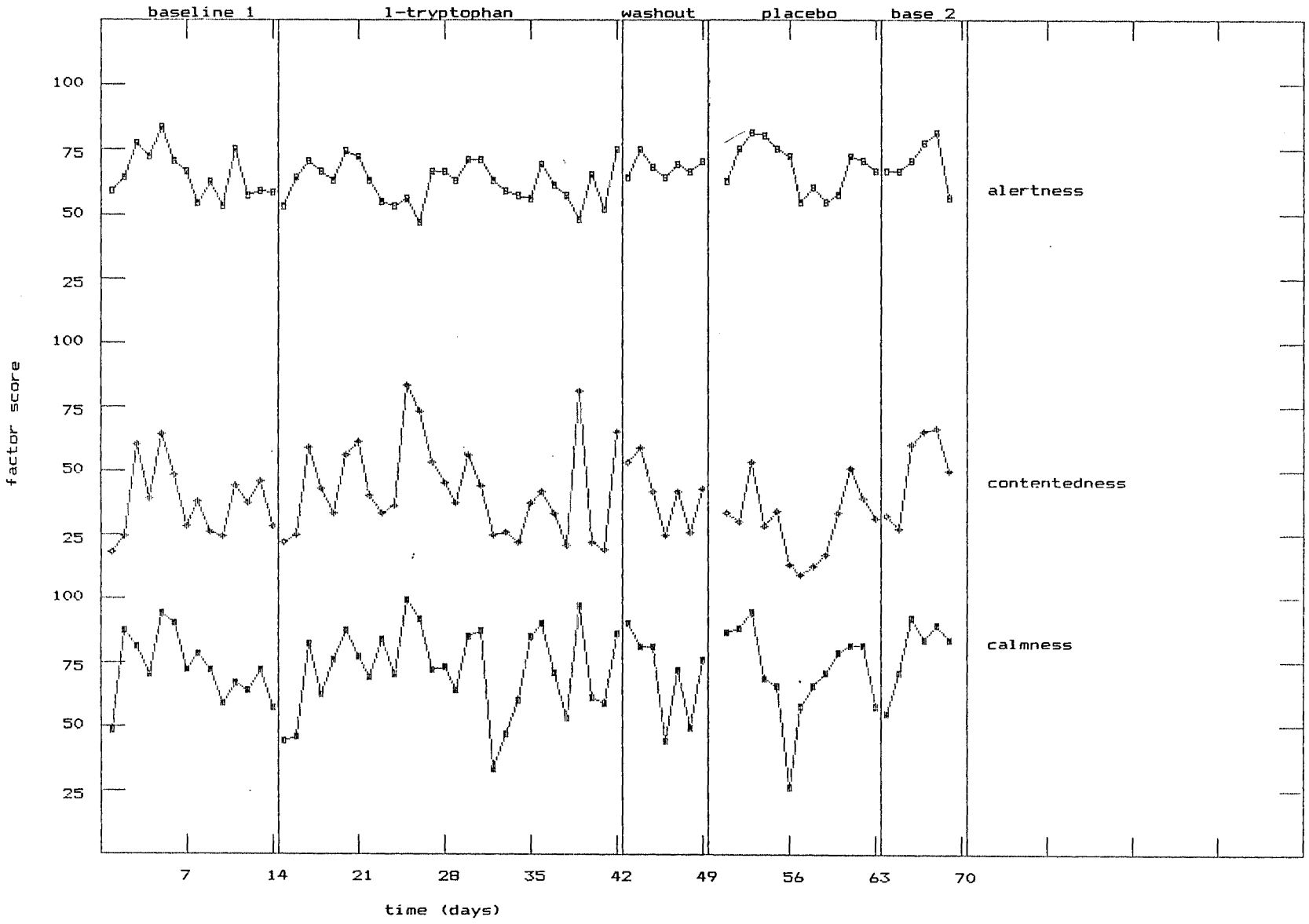


Table 4-9-3 continued:

factor	placebo(n=13)		
	r1	r2	r3
alertness			
morning	-.21	.06	-.11
evening	.57**	.20	-.14
cont...ss			
morning	-.42	.13	-.07
evening	.46*	.17	-.34
calmness			
morning	-.12	.05	-.04
evening	.42*	.14	-.36

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Table 4-9-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	0.13 ns	~-1.58 ns	~-2.49 *+
evening	1.84 ns	-0.73 ns	-2.00 ns
contentedness			
morning	-0.90 ns	-0.24 ns	0.71 ns
evening	-2.36 *	1.49 ns	2.27 *+
calmness			
morning	~-1.15 ns	-1.00 ns	~-0.14 ns
evening	-0.08 ns	0.29 ns	0.23 ns

* exceeds critical value for the .05 level of significance

+ sig. t values affected by sig. levels of autocorrelation

- indicates the first mean of the pair is the lowest

Comment on t statistic results

Significant differences were limited to lower means for morning alertness during baseline and tryptophan phases relative to placebo. There was also an increase in the contentedness mean

for tryptophan relative to baseline and placebo in the evening. Positive autocorrelation in the morning tryptophan phase for alertness may have led to an over-estimation of the significance of the placebo - tryptophan difference for this dimension.

C statistic results

Table 4-9-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	1.11 ns	0.71 ns
cont...ss	1.48 ns	1.32 ns
calmness	1.83 *	~ 2.15 *
evening		
alertness	1.06 ns	0.71 ns
cont...ss	0.67 ns	1.34 ns
calmness	1.83 *	~ 1.46 ns

* exceeds the critical value for the .05 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see Chapter III for explanation)

Comment on C statistic results

The only significant result was for a departure in trend for tryptophan versus baseline on the morning calmness series.

(c) Hours of sleep

Table 4-9-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=21)				placebo(n=14)		
r1	r2	r3	r1	r2	r3	r4	r1	r2	r3
.17	-.28	-.10	.00	-.19	-.11	.24	-.49*	.09	-.02

* exceeds the critical value for the .05 level of significance

t test results for hours of sleep

base1 - tryp	bas1 - tryp	tryp - plac
0.71 ns	0.26 ns	-0.51 ns

Comment on hours of sleep

No significant changes emerged for mean hours of sleep between baseline, tryptophan or placebo phases.

(d) Side effects

A low level of reported side effects was maintained by this subject throughout baseline and tryptophan phases; the mean severity of effects being 0.43 and 0.17 respectively. Thus, there was a slight decline during the tryptophan phase (relative to baseline) despite this subjects consumption of the maximum 6gms/day dose for 28 days. Some rise in severity was noted for the placebo phase i.e. mean = 1.3 with 7 reports of dry mouth being the most prominent feature. No other qualitative differences between phases could be discerned for this subject and no other symptom was reported more than twice in one phase.

(5) Summary and Conclusions

Due to a motivation of depression for participation and the high anxiety scores for this subject, attention was given to therapeutic effects. Appraisal of weekly total scores on anxiety and depression indicated no evidence of consistent change with respect to tryptophan intake. Rather, there was a marked increase in reports of anxiety symptoms during the washout and placebo phases relative to the rest of the series as indicated by State scores and the anxiety dimension of the HSCL. This increase could not be meaningfully related to experimental conditions and did not show any coincidence with reports of unusual happenings.

As is evident from Figures 4-9-1 and 4-9-2, both morning and evening series were characterized by high day to day variability and no evidence of between or within phase changes for any dimension were apparent. The significantly lower mean for the tryptophan phase relative to placebo on morning alertness may have been overestimated due to the presence of positive autocorrelation in the tryptophan period. Also, there was no significant reduction in alertness for the morning tryptophan

phase relative to baseline. The statistically significant mean increase in contentedness during the evening tryptophan phase, relative to baseline and placebo, was not supported by visual analysis. The statistically significant departure in trend for tryptophan relative to baseline on the evening calmness dimension was based on the less powerful C statistic application which used only the first half of the tryptophan phase. Visual analysis did not support this finding as being of psychological significance.

Thus, results for the present subject were not supportive of a therapeutic action for tryptophan. No general mood altering effects could be associated with tryptophan intake, nor was there any indication of an increase of side effects or change in total sleep time associated with this phase.

4.2.10 Subject 10

(1) Demographic variables

age(yrs): 42 sex: male height(cms):152
weight(kgs):60.00
(above desirable weight range)

tryptophan experience: not consumed prior to this project
motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial SDS score for this subject was within one standard deviation of Knight et al.'s (1983) norm and two of the remaining four SDS scores slightly exceeded the one standard deviation limit. However, such elevated scores were not sufficient to achieve a depression classification based on Zung's (1972) criteria. On this basis and the motivation for participation of general interest, the present subject was considered 'non depressed'.

(b) Anxiety status

This subject commented on experiencing occasional high levels of anxiety and fustration. With respect to Knight et al.'s (1983) norms the Trait anxiety score (40) almost exceeded one standard deviation above the normal mean for the appropriate age category (Knight et al., 1983). Thus, the present subject was considered to exhibit slightly above normal levels of anxiety.

(3) Experimental variables

(a) Dose level(gms/day): 2

(b) Phase description

baseline 1	tryptophan	washout
14days	14days	7 days

(c) Extra details

Scale completion time was regular with no missing data accrued. No tryptophan or placebo tablets were forgotton.

(4) Results and analysis

(a) Weekly scores

Table 4-10-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash
day	01	07	14	21	28	35
scale						
zung	37	39	38	33	-	26
state	39	37	36	40	-	37
HSCL	100	97	97	93	-	89

Table 4-10-2 HSCL factor scores

	baseline 1			tryptophan		wash
day	01	07	14	21	28	35
factor						
1	1.31	1.23	1.36	1.29	-	1.08
2	2.26	2.11	2.34	2.07	-	1.84
3	2.30	2.14	1.98	1.98	-	1.98
4	1.54	1.54	1.61	1.61	-	1.16
5	1.44	1.44	1.44	1.59	-	1.44

Comment on weekly scale scores

No particular changes were noted during the first week of tryptophan consumption relative to the baseline phase. Similarly, there were no clear alterations apparent from the HSCL factor scores. Scores for HSCL factors 2 and 3 were close to means for a depressed sample, while factors 1, 4 and 5 were closer to the normal group (Table 3-4).

(b) Mood factors

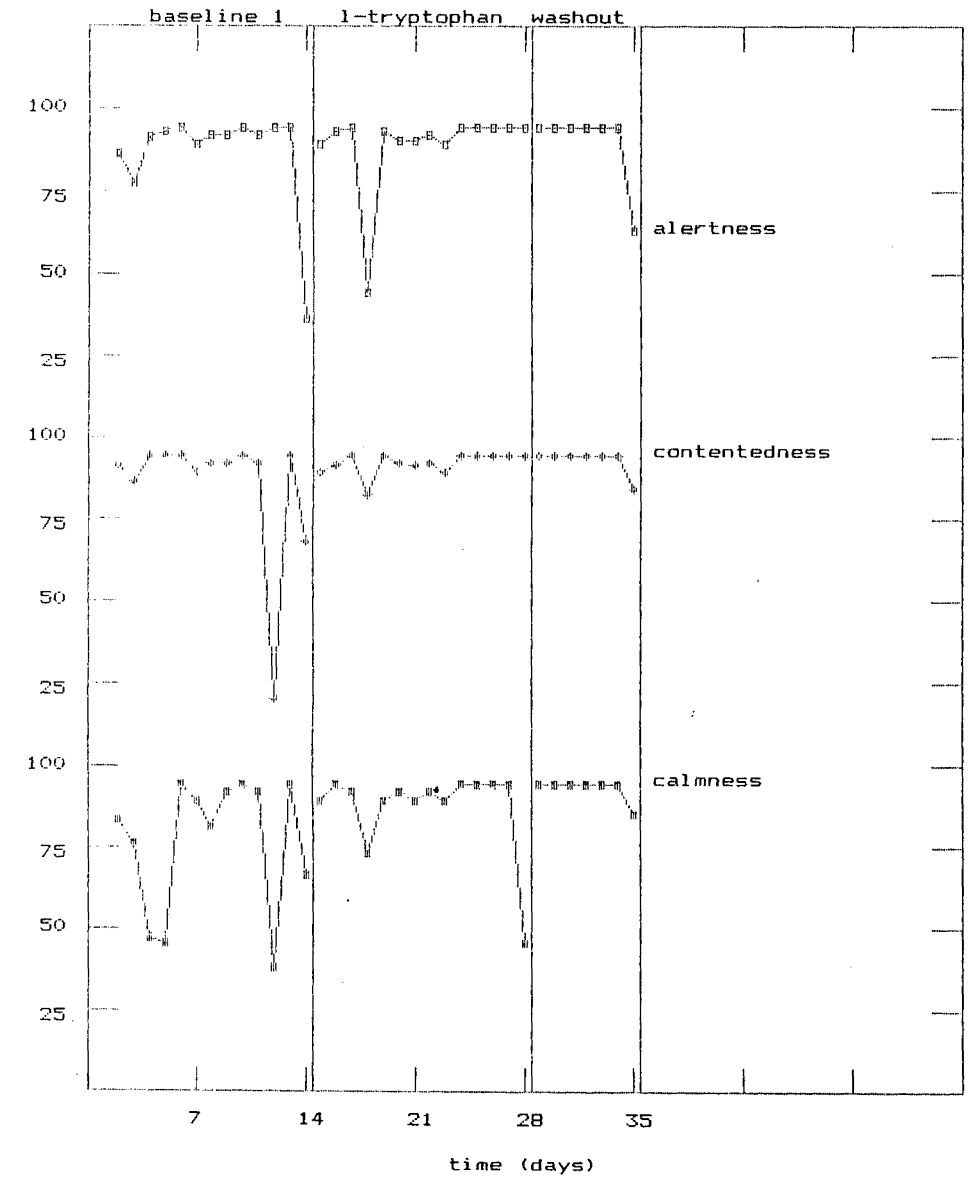
Visual analysis of graphed data

Both morning and evening series are presented in Figure 4-10 for this subject. There was a lack of consistent change with respect to level or trend between or within phases for either series. However, the marked decline in ratings on day 11 of baseline 1 coincided with veiwing of a film on nuclear war the previous evening, which aroused anger and fustration. No other reports of unusual happenings or side effects were noted which could be related to subsequent dips in ratings for the morning series. The marked dip on day seven of the evening series coincided with the receipt of an emotionally arousing letter.

Figure 4-10

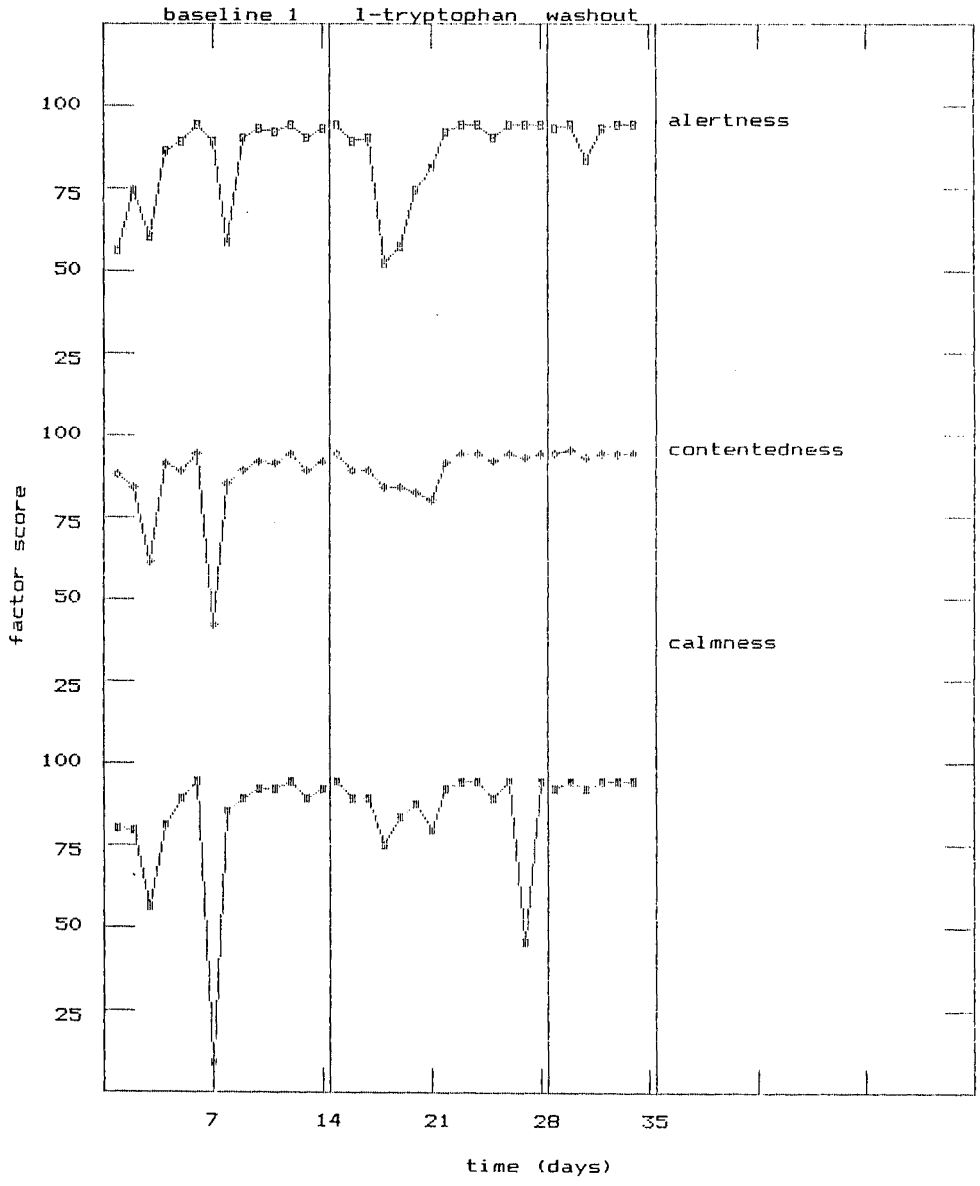
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 10



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 10



Autocorrelation estimates

Table 4-10-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=14)		
	r1	r2	r3	r1	r2	r3
alertness						
morning	-.03	-.06	-.04	-.13	-.05	.02
evening	.23	.15	-.14	.59**	.17	-.16
cont...ss						
morning	-.15	.19	-.03	-.20	.09	.24
evening	-.10	-.11	-.22	.64**	.34	.004
calmness						
morning	-.15	.19	-.03	-.06	-.12	-.08
evening	-.08	-.12	-.10	-.23	.01	-.14

** exceeds the critical value for the .01 level of significance

t test results

Table 4-10-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp
alertness	
morning	-0.43 ns
evening	-0.55 ns
contentedness	
morning	~-1.23 ns
evening	~-1.26 ns
calmness	
morning	-0.38 ns
evening	~-0.78 ns

Comment on t test results

As evident from Table 4-10-4, no significant mean differences were detected between baseline and tryptophan phases.

C statistic results

Table 4-10-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	1.52 ns	-0.46 ns
cont...ss	-0.47 ns	-0.50 ns
calmness	-0.47 ns	-0.04 ns
evening		
alertness	1.55 ns	2.77 **
cont...ss	-0.34 ns	0.30 ns
calmness	-0.27 ns	-0.41 ns

** exceeds the critical value for the .01 level of significance

Comment on C statistic results

The only significant finding, as indicated in Table 4-10-5, was for a departure in trend for the evening tryptophan phase relative to baseline on alertness.

(c) Hours of sleep

The present subject failed to consistently respond to the hours of sleep question, consequently only two tryptophan recordings were obtained which made comparison of phases inappropriate.

(d) Side effects

There was a consistent lack of side effects reported by this subject throughout the trial. Only one headache and one increased appetite were noticed during baseline 1.

(5) Summary and Conclusions

The validity of results for this subject was limited by the absence of a placebo phase. However, there was no indication of consistent changes on either weekly scales or daily mood dimensions between baseline and tryptophan phases. As indicated

earlier, this subject exhibited slightly elevated levels of anxiety (relative to Knight et al.'s (1983) norms). There were, however, no indications of changes in this state in association with tryptophan ingestion. The one statistically significant finding for this subject was for a significant departure in trend for the evening tryptophan phase relative to baseline on the alertness dimension. A clear dip over 3-4 days is apparent in this series (Figure 4-10). No increase in reported side effects was apparent for the tryptophan period. Thus, there was a lack of consistent change (relative to baseline) in general mood, side effects or anxiety levels associated with the low (2gms/day) tryptophan dose in this subject.

4.2.11 Subject 11

(1) Demographic variables

age(yrs): 33 sex: female height(cms):158
weight(kgs):48.00
(within desirable weight range)

PMT?: yes
l-tryptophan experience: - not consumed prior to this project
motivation for participation: - depression

(2) Psychological variables

(a) Depression status

For this subject, the initial and most subsequent SDS total scores exceeded one standard deviation above the mean relative to Knight et al.'s (1983) norms. In addition, all scores fell within Zung's (1972) 'mild-moderate' depression category. Thus, on the basis of relatively elevated SDS scores and the motivation for participation, the present subject was classed as depressed.

(b) Anxiety Status

The Trait anxiety score for this subject exceeded one standard deviation above the mean with respect to Knight et

al.'s (1983) norms. The initial State score for this subject was extremely elevated with respect to the above norms i.e. 3 standard deviations above the appropriate mean, while subsequent scores varied between 1-2 standard deviations above the respective mean. Consequently, the present subject was considered to exhibit relatively high, fluctuating levels of State anxiety, in keeping with predictions based on the high Trait score.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	14days	7days	14days	7days

(c) Extra details

Scale completion time was regular with only one morning mood scale rating missed towards the end of the tryptophan period. No tablets (trytophan/placebo) were forgotten.

4.2.11.4 Results and analysis

(a) Weekly scores

Table (4-11-1) Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56
scale									
zung	-	48	48	45	47	47	43	47	43
state	-	67	54	49	57	52	48	48	49
HSCL	-	100	111	92	113	99	89	93	92

Table 4-11-2 HSCL factor scores

	baseline		1	tryptophan		wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56
factor									
1	-	1.59	1.65	1.39	2.26	1.77	1.62	1.49	1.38
2	-	1.93	2.06	1.69	1.69	1.69	1.67	1.94	1.84
3	-	1.62	1.90	1.34	1.46	1.34	1.16	1.34	1.32
4	-	1.81	1.90	1.53	1.61	1.80	1.52	1.53	1.72
5	-	1.31	1.62	1.72	1.71	1.42	1.00	1.15	1.31

Comment on weekly scale scores

A slight reduction in State anxiety and HSCL total scores was apparent over the whole trial. However, there was no evidence of between phase changes for these scores or for Zung total scores. The slight reduction in HSCL scores noticeable during the second half of the trial appeared most attributable to factor 5, i.e. anxiety. This is in keeping with the reduction in State scores over the same period. HSCL factor scores were elevated relative to the normal sample and in some cases were more in keeping with means for an anxious sample (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

Relatively high day to day variability marked both series (Figures 4-11-1 and 4-11-2) for this subject, with no systematic variation between or within phases, except for a slight overall reduction in the evening alertness level relative to basline and placebo periods. Little difference was apparent in the level or variability between morning and evening series. The reporting of unusual or traumatic events such as being woken at night coincided quite consistently with depressed mood ratings, e.g. the 1st, 10th and 14th baseline days days all coincided with the only reports of unusual events during this phase. Similar coincidences were noted on the 3rd and 4th days of this period.

Figure 4-11-i

FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 11

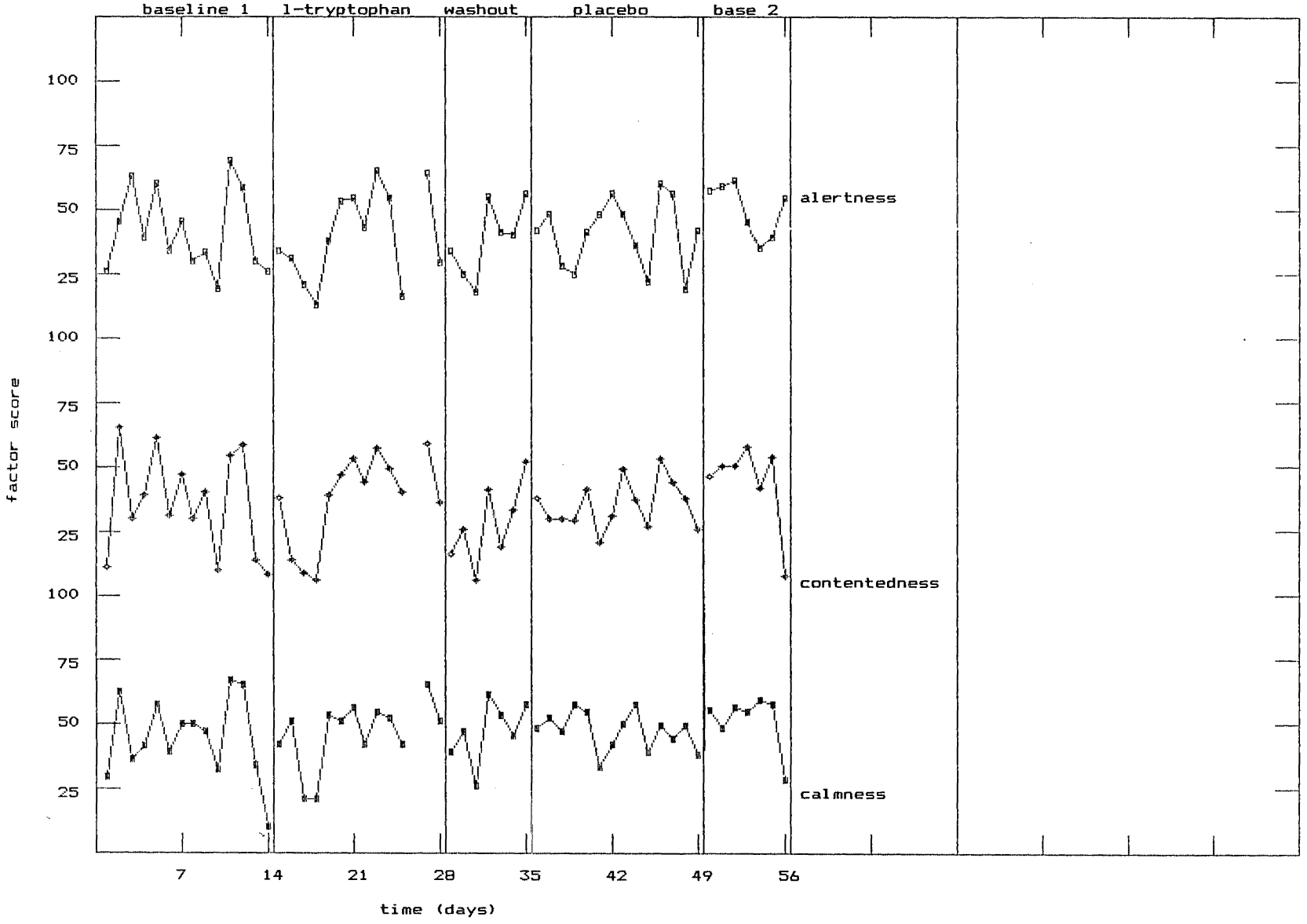
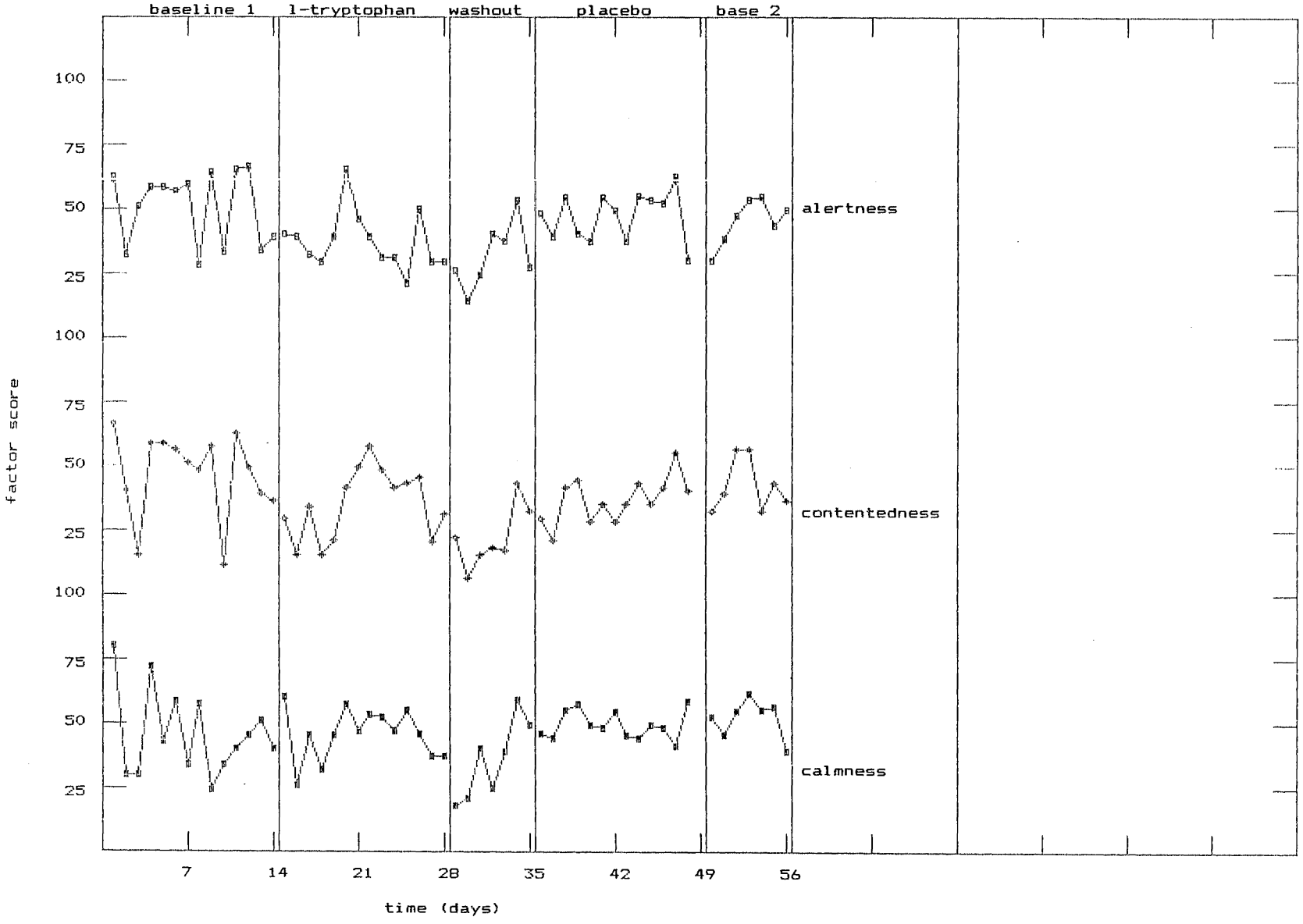


Figure 4-11-2
FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 11



Autocorrelation estimates

Table 4-11-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=28)		
	r1	r2	r3	r1	r2	r3
alertness						
morning	-.05	-.22	-.28	.07	.12	.12
evening	-.34	-.05	-.09	.14	-.14	-.24
cont...ss						
morning	-.22	-.18	.06	.58**	.31	-.01
evening	-.23	-.27	.01	.49**	.24	.07
calmness						
morning	-.06	-.36	-.05	.18	-.08	.01
evening	-.30	-.05	.06	.49**	.23	.07

Table 4-11-3 continued:

factor	placebo(n=14)		
	r1	r2	r3
alertness			
morning	-.02	-.52*	-.08
evening	-.28	-.14	.23
cont...ss			
morning	-.05	-.31	.20
evening	.46*	.25	.08
calmness			
morning	-.10	-.25	-.21
evening	-.10	-.26	.17

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Comment on t test results

As demonstrated in Table 4-11-4, the only significant findings were for a lower mean during the evening tryptophan phase relative to placebo and baseline periods. These findings were not affected by the presence of significant autocorrelation.

Table 4-11-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1- plac	tryp - plac
alertness			
morning	0.25 ns	0.08 ns	-0.20 ns
evening	2.81 **	0.80 ns	-2.46 *
contentedness			
morning	-0.30 ns	~ 0.05 ns	~ 0.47 ns
evening	1.96 ns	~ 1.90 ns	~-0.36 ns
calmness			
morning	-0.36 ns	~-0.62 ns	~-0.21 ns
evening	1.88 ns	~-0.74 ns	~-1.14 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

~ indicates the first mean of the pair is the lowest

C statistic results

Table 4-11-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	0.08 ns	0.29 ns
cont...ss	-0.36 ns	0.80 ns
calmness	0.64 ns	0.43 ns
evening		
alertness	-1.16 ns	0.79 ns
cont...ss	-0.63 ns	1.19 ns
calmness	-0.50 ns	1.22 ns

Comment on C statistic results

As is apparent from Table 4-11-5, no significant departures in trend were evident for tryptophan periods relative to baseline.

(c) Hours of sleep

Table 4-11-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=13)			placebo(n=14)		
r1	r2	r3	r1	r2	r3	r1	r2	r3
-.06	.25	-.20	.49*	-.11	-.30	.10	-.36	-.11

* exceeds the critical value for the .05 level of significance

t test value results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
~-0.23 ns	~-0.69 ns	~-1.23 ns

Comment on hours of sleep

No significant changes emerged for hours of sleep in terms of the mean difference between baseline, tryptophan and placebo phases.

(d) Side effects

Table 4-11-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=14)			placebo(n=13)		
r1	r2	r3	r1	r2	r3	r1	r2	r3
.50**	.12	-.05	.22	-.24	-.30	.26	-.16	.12

** exceeds the critical value for the .01 level of significance

t test results for side effect severity

base1 - tryp	base1 - plac	tryp - plac
~-3.57 **	-2.51 *	2.20 *

Comment on side effects

As is evident from the t test results, both tryptophan and placebo periods exhibited significant elevations in side effect severity relative to baseline. The most severe levels were attained during the tryptophan phase which exhibited a

significantly higher level than the placebo period. The rise in tryptophan phase levels was associated with qualitative changes relative to baseline and placebo. That is, frequent reports of constipation (9 times) and increased appetite (7 times) were unique to this period.

(e) Premenstrual tension

The first onset of menstruation for this subject was noted on day 8 of the tryptophan phase and lasted for three days. Thus, it is difficult to determine how much of the increased incidence in side effect levels (associated with the tryptophan phase) should be attributed to possible premenstrual symptoms. However, the high level of negative symptoms experienced at this time continued into the post menstrual phase, while tryptophan was still being consumed. This subject began menstruating again on the last day of baseline 2: the mean severity of side effects for the associated premenstrual phase was 1.5 which was identical to the first premenstrual phase. Since the two phases were comparable, it might be assumed that premenstrual symptoms could not account for the overall elevation in side effect severity associated with the tryptophan phase.

(5) Summary and Conclusions

As indicated previously this subject was classed as depressed relative to other participants. More significant than the depressive symptomatology exhibited by this subject, however, were the high levels of anxiety as measured by the State scales. There was a slight decline on State anxiety scores and the HSCL anxiety factor for the second half of the trial period. However, no change in relation to the tryptophan phase versus other periods was apparent. Statistical analysis indicated a significant reduction in the level of evening alertness for the tryptophan versus placebo and baseline periods which was also detected by visual analysis.

The most noticeable effect during the tryptophan phase, was for a signficant increase in the level of side effects. As discussed previously part of the tryptophan period coincided with

a premenstrual phase for this subject. However, comparison of both premenstrual phases indicated that the rise in symptom severity could not be confidently accounted for by the premenstrual phase alone. In addition, tryptophan intake and high levels of side effects continued for some days after the premenstrual phase. Although the placebo phase demonstrated an elevation in side effects relative to baseline, the tryptophan phase was still associated with the highest significant level.

Thus, intake of 3gms/day of tryptophan for this subject was associated with a reduction in alertness and an increase in side effects - particularly constipation and increased appetite. There was no evidence of therapeutic effects associated with tryptophan intake with respect to reduction in depressive or anxious symptomatology as measured by the weekly and daily scales.

4.2.12 Subject 12

(1) Demographic variables

age(yrs): 31 sex: female height(cms):166
weight(kgs):54.00
(within desirable weight range)

chemical contraceptives?: yes
PMT?: yes
l-tryptophan experience: - not consumed prior to this project
motivation for participation: - depression

(2) Psychological variables

(a) Depression status

The initial and several subsequent SDS total scores for this subject exceeded one standard deviation above the mean according to Knight et al.'s (1983) norms. On the basis of Zung's (1972) criteria the first SDS score for this subject could be considered to lie within the 'moderate to severe' depression category. Most subsequent elevated scores, however, only reached the 'mild -

moderate' division. The present subject was consequently classed as depressed.

(b) Anxiety Status

The present subject exhibited a Trait anxiety score (70) greater than three standard deviations above the appropriate age and sex mean according to Knight et al.'s (1983) norms. The initial and most subsequent State scores exceeded two standard deviations above the respective mean. Consequently the present subject was considered to exhibit high levels of State anxiety throughout the trial in keeping with the initial Trait total.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	28days	7days	14days	7days

(c) Extra details

Scale completion time was regular with little missing data accrued. No tablets (trytophan/placebo) were forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-12-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan				wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56	63	70
scale											
zung	47	-	49	42	44	38	42	48	45	38	37
state	58	-	68	51	51	48	52	71	56	51	45
HSCL	140	-	131	117	107	103	111	130	117	107	95

Table 4-12-2 HSCL factor scores

	baseline 1				tryptophan			wash	placebo		bs2
day	01	07	14	21	28	35	42	49	56	63	70
factor											
1	1.65	-	1.34	1.77	1.60	1.77	1.41	1.40	1.24	1.44	1.15
2	3.27	-	3.15	2.79	2.67	2.63	2.90	2.78	2.90	2.67	2.18
3	2.75	-	3.03	2.46	2.14	2.37	1.88	2.64	2.33	2.13	2.04
4	2.64	-	2.40	1.76	1.70	1.78	1.95	2.52	2.06	1.52	1.79
5	2.37	-	2.50	1.93	1.62	1.47	1.90	2.52	2.19	1.91	1.47

Comment on weekly scale scores

There was a slight decline in Zung scores during the tryptophan phase relative to baseline and washout. A more noticeable decline was apparent in State and HSCL total scores during the tryptophan relative to baseline phase, followed by a rise in both scores during the washout period. However, the decline for the tryptophan period on all scales was no greater than that for the placebo phase. Most of the decline associated with the HSCL scores was attributable to factors 4 and 5, that is: depression and anxiety respectively, which is in keeping with the SDS and State trends. HSCL factor scores were most in keeping with means for a depressed sample (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

Examination of the morning (Figure 4-12-1) and evening (Figure 4-12-2) series indicated high day to day variability for alertness with no obvious changes within or between phases. There was evidence that the evening and to a lesser extent the morning contentedness dimension stabilized at a higher level (during the tryptophan phase) than that for the baseline period. However, there was no elevation with respect to the placebo phase. Consistency in the level and variability of ratings was apparent between morning and evening series. The large dip on calmness in both series (day 11 of baseline) coincided with a report by this subject of the sexual abuse of her son.

Figure 4-12-1
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 12

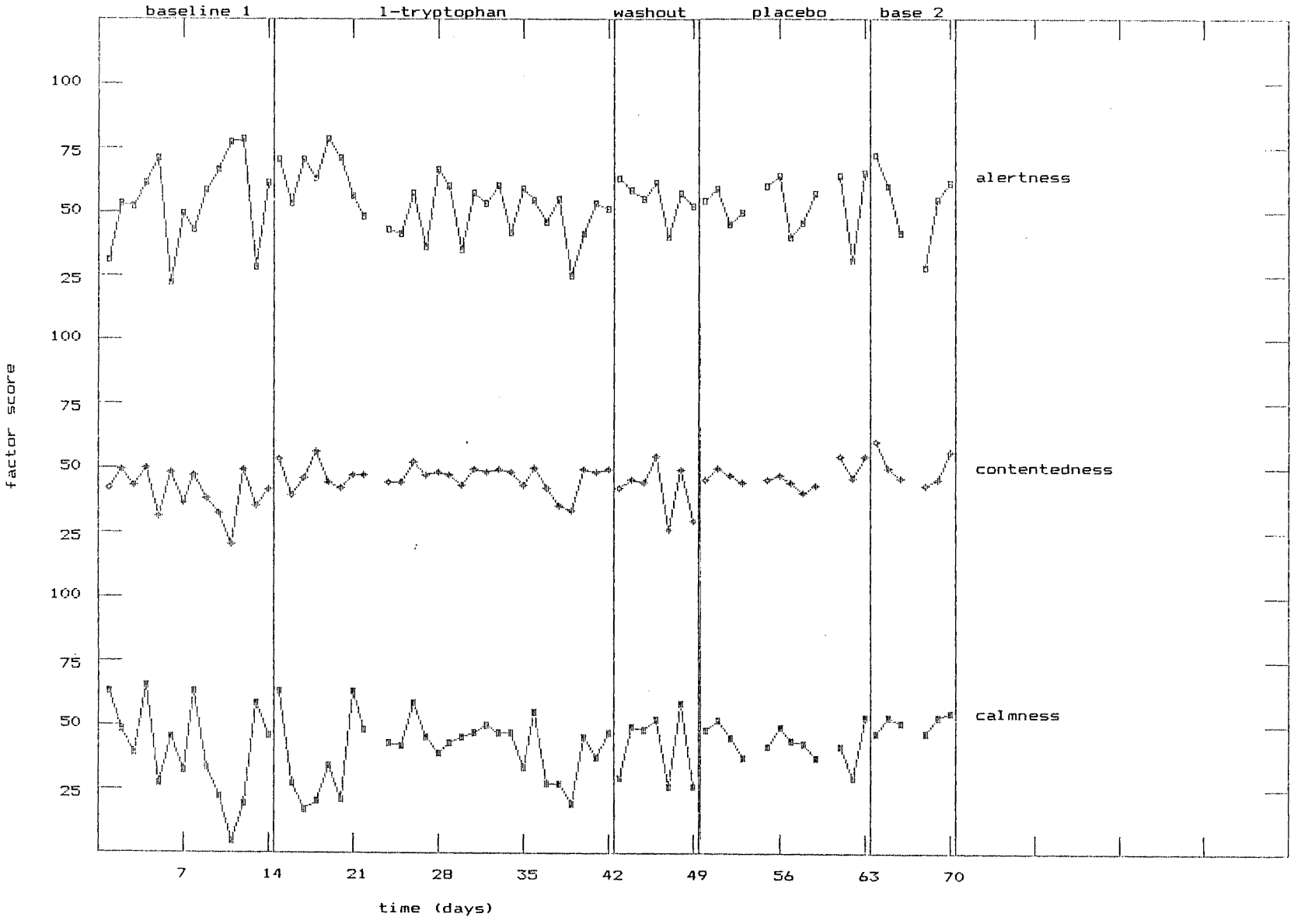
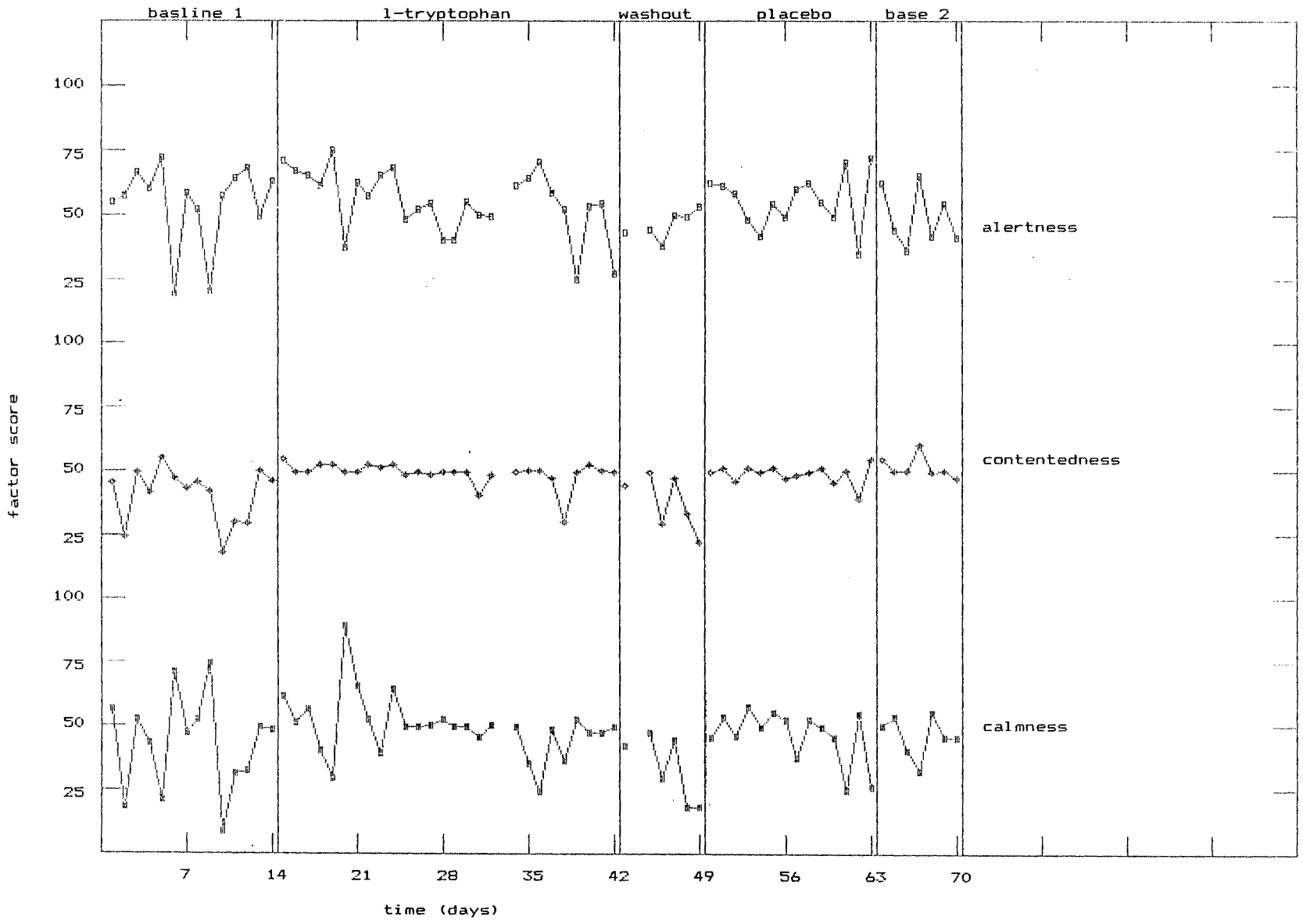


Figure 4-12-2

FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 12



Autocorrelation estimates

Table 4-12-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=28)			
	r1	r2	r3	r1	r2	r3	r4
alertness							
morning	-.04	-.03	-.21	.19	.26	.15	.02
evening	-.16	-.06	.13	.18	.13	.15	.10
cont...ss							
morning	-.22	.28	-.27	.10	-.22	.02	-.12
evening	.12	.13	-.33	.12	-.14	-.08	-.13
calmness							
morning	.14	.01	-.25	.18	.13	-.13	.04
evening	-.28	-.05	.13	.05	-.10	-.02	.22

Table 4-12-3 continued:

factor	placebo(n=14)		
	r1	r2	r3
alertness			
morning	-.40	-.29	.03
evening	-.41	.23	-.13
cont...ss			
morning	.01	.04	-.14
evening	-.54*	.29	-.30
calmness			
morning	-.11	-.03	-.25
evening	-.22	.35*	.03

* exceeds the critical value for the .05 level of significance

t test results

Comment on t test results

The means of the tryptophan and placebo periods were significantly higher than baseline in both morning and evening series for contentedness (Table 4-12-4). Significant negative autocorrelation in the evening seris for contentedness may have led to an overestimation of significance for the baseline -tryptophan difference for this dimension.

Table 4-12-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	0.03 ns	0.11 ns	0.13 ns
evening	-0.12 ns	-0.24 ns	-0.17 ns
contentedness			
morning	~-2.78 **	~-2.69 *	-0.35 ns
evening	~-2.80 *	~-2.72 *+	0.10 ns
calmness			
morning	-0.01 ns	~-0.59 ns	0.06 ns
evening	~-1.09 ns	~-0.53 ns	0.80 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

\+ sig. t values affected by sig. levels of autocorrelation

\- indicates the first mean of the pair is the lowest

C statistic results

Table 4-12-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	0.11 ns	0.80 ns
cont...ss	-0.88 ns	0.46 ns
calmness	0.83 ns	1.36 ns
evening		
alertness	-0.60 ns	0.64 ns
cont...ss	0.58 ns	2.23 *
calmness	-1.03 ns	-0.49 ns

** exceeds the critical value for the .01 level of significance

Comment on C statistic results

As indicated in Table 4-12-5, the contentedness dimension exhibited a significant departure in trend from the baseline phase in the evening series only.

(c) Hours of sleep

Table 4-12-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=13)			tryptophan(n=23)				placebo(n=11)	
r1	r2	r3	r1	r2	r3	r4	r1	r2
-.65**	.16	.06	-.23	-.17	.09	.08	.28	-.01

** exceeds the critical value for the .01 level of significance

t test value results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
-0.75 ns	0.18 ns	0.92 ns

Comment on hours of sleep

No significant changes emerged for hours of sleep in terms of the mean difference between baseline, tryptophan or placebo phases.

(d) Side effects

Table 4-12-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=27)				placebo(n=143)		
r1	r2	r3	r1	r2	r3	r4	r1	r2	r3
-.01	-.01	-.02	.48	.22	.18	.19	-.32	.20	-.12

None of the above estimates proved significant

t test value results for side effect severity

base - tryp	base - plac	tryp - plac
-7.43 **	~-3.32 **	~ 2.46 *

Comment on side effects

As is evident from the t test results, both tryptophan and placebo periods were associated with higher levels of side effects than baseline, but the severity level for the tryptophan phase remained higher than that of placebo. The main qualitative

change in symptoms associated with the tryptophan phase was the unique and frequent reporting of constipation. Other symptoms demonstrating marked increases during the tryptophan phase were appetite and headaches.

(e) Premenstrual Tension

The present subject was menstruating during the first five days of baseline 1, thus, the associated premenstrual phase could not be assessed. The second onset of menstruation was noted on day 15 of the trytophan phase and continued for four days. The third and final menstrual onset for the trial period was noted on day 7 of the placebo phase and lasted three days. The mean severity of side effects for the first premenstrual phase (during tryptophan administration) was 2 compared to 1.2 for the second premenstrual phase. Consequently, there is a need to interpret the rise in side effects associated with tryptophan cautiously given coincidence of the premenstrual period with the first half of this phase.

(5) Summary and Conclusions

As indicated previously, the present subject was considered to be experiencing moderate depression and much higher than normal levels of anxiety. There was some evidence of a reduction in anxiety symptoms as measured by the State anxiety scale and the anxiety dimension of the HSCL during the tryptophan period relative to the first baseline phase. However, the reduction of scores was of a similar magnitude to that expressed during the placebo period. The visual indication of an increase in contentedness - particularly during the evening - was supported by statistical evidence of increased tryptophan versus baseline means. In addition, a significant departure in trend for the tryptophan relative to baseline phase was indicated following application of the C statistic for, the contentedness dimension in the evening series. However, as evident from both statistical and visual anaylses the increase was not maintained relative to the placebo phase.

The statistically significant increase in the level of side

effects associated with the tryptophan phase relative to baseline and placebo needs to be interpreted cautiously due to the coincidence of a premenstrual phase with the first two weeks of tryptophan intake. Compared to the second premenstrual phase, the level of symptoms in the first case was higher, indicating that tryptophan intake could have been responsible for at least part of the rise. The fact that increased consitpation and an extreme elevation in the frequency of increased appetite (i.e. on 19 out of 28 days) were unique to the tryptophan period does indicate such changes could be attributable to tryptophan intake. Thus, therapeutic effects above placebo were not supported following consumption of 3gms/day of tryptophan for 28 days by this subject. Large increases in reported side effects - particularly constipation and increased appetite were uniquely associated with the tryptophan phase.

4.2.13 Subject 13

(1) Demographic variables

age(yrs): 46 sex: female height(cms):166
weight(kgs):50.80
(within desirable weight range)

PMT?: yes
tryptophan experience: - not consumed prior to this project
motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial SDS total score for the present subject was below the appropriate mean according to Knight et al.'s (1983) norms and subsequent scores throughout the trial remained within one standard deviation of this value. On this basis and given the general interest motivation for participation the present subject was considered non depressed.

(b) Anxiety status

The Trait score (28) for this subject was low relative to Knight et al.'s (1983) norm, that is, under one standard deviation below the mean. The initial State score was also below the appropriate mean with subsequent scores remaining within one standard deviation from the mean. Consequently this subject was considered free from significant levels of anxiety.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	14days	7days	14days	7days

(c) Extra details

Scale completion time was regular with missing data confined to one morning and one evening rating at the end of the tryptophan and baseline 2 phases respectively. No tablets (trytophan/placebo) were forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-13-1 Total scores for Zung, State Anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo	
day	01	07	14	21	28	35	42	49
scale								
zung	28	30	31	30	40	40	32	26
state	27	35	29	26	32	45	31	28
HSCL	70	74	77	79	103	90	64	65

Table 4-13-2 HSCL factor scores

	baseline 1			tryptophan		wash	placebo	
day	01	07	14	21	28	35	42	49
factor								
1	1.27	1.26	1.42	1.15	2.32	1.78	1.09	1.07
2	1.40	1.52	1.40	1.37	1.91	1.37	1.00	1.00
3	1.34	1.47	1.29	1.62	1.13	1.34	1.18	1.00
4	1.00	1.28	1.46	1.46	2.10	1.57	1.10	1.10
5	1.16	1.00	1.00	1.31	1.00	1.15	1.00	1.15

Comment on weekly scale scores

As is evident from Table 4-13-1, there was a slight elevation in all weekly scores during the second week of trytophan intake and during the washout phase relative to the rest of the trial. While this subject was not considered to be particularly anxious, the State total score and the HSCL anxiety factor demonstrated sensitivity for this individual. However, the elevation in Zung scores was not supported by elevation in the HSCL depression dimension. Thus, the elevation in Zung total scores may have been attributable to the increase in anxiety and somatic symptoms (supported by the HSCL dimensions exhibiting most increase at this time)rather than depressed mood. HSCL factor scores were most in keeping with means for a normal sample (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

The most consistent feature apparent from examination of Figures 4-13-1 and 4-13-2 concerned the declines on contendedness and alertness in both series during the last 4 days of tryptophan consumption. This decline coincided with reports of severe flu symptoms over the same period. No meaningful changes between or within phases could otherwise be detected by the present author.

Figure 4-13-1
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 13

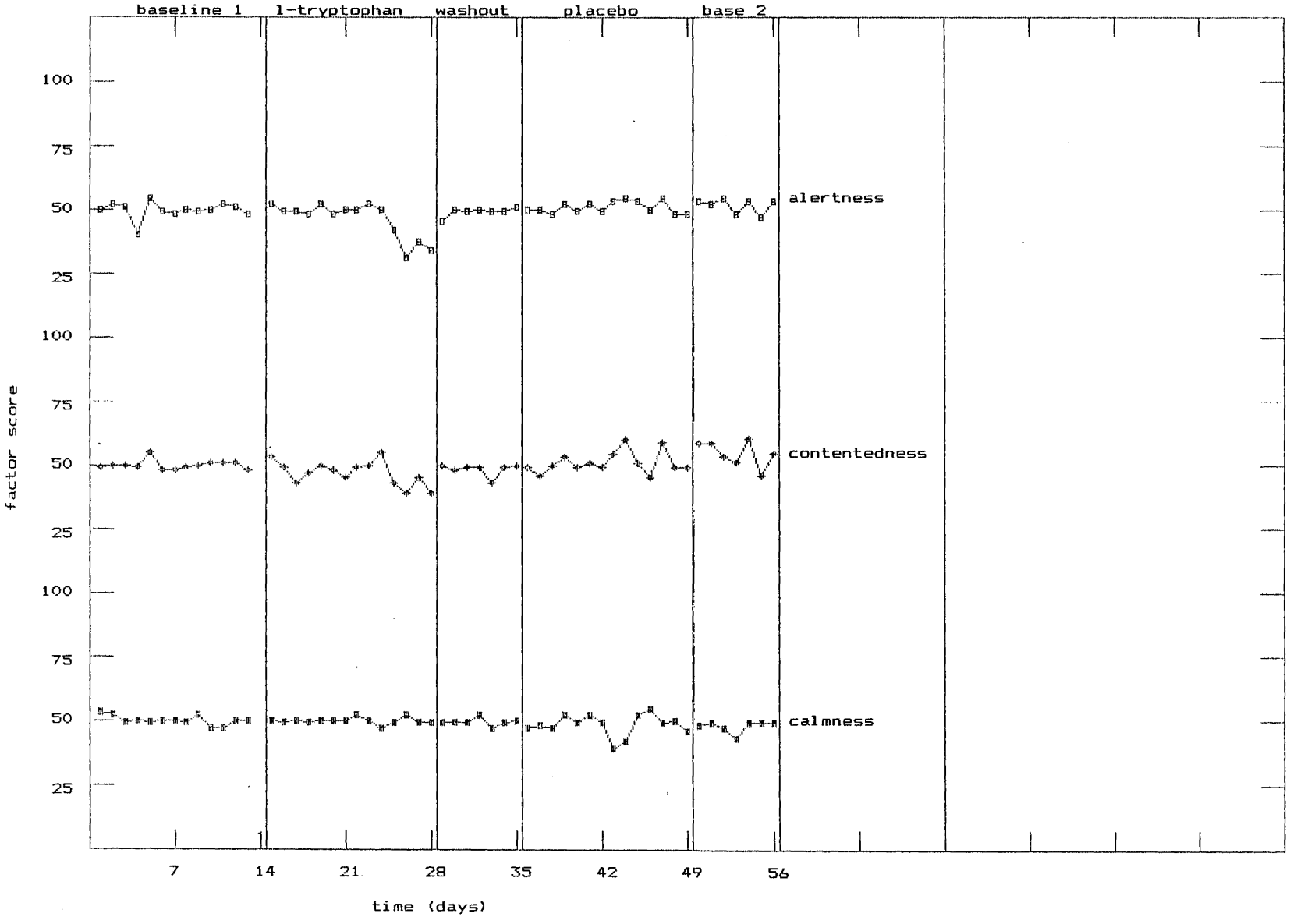
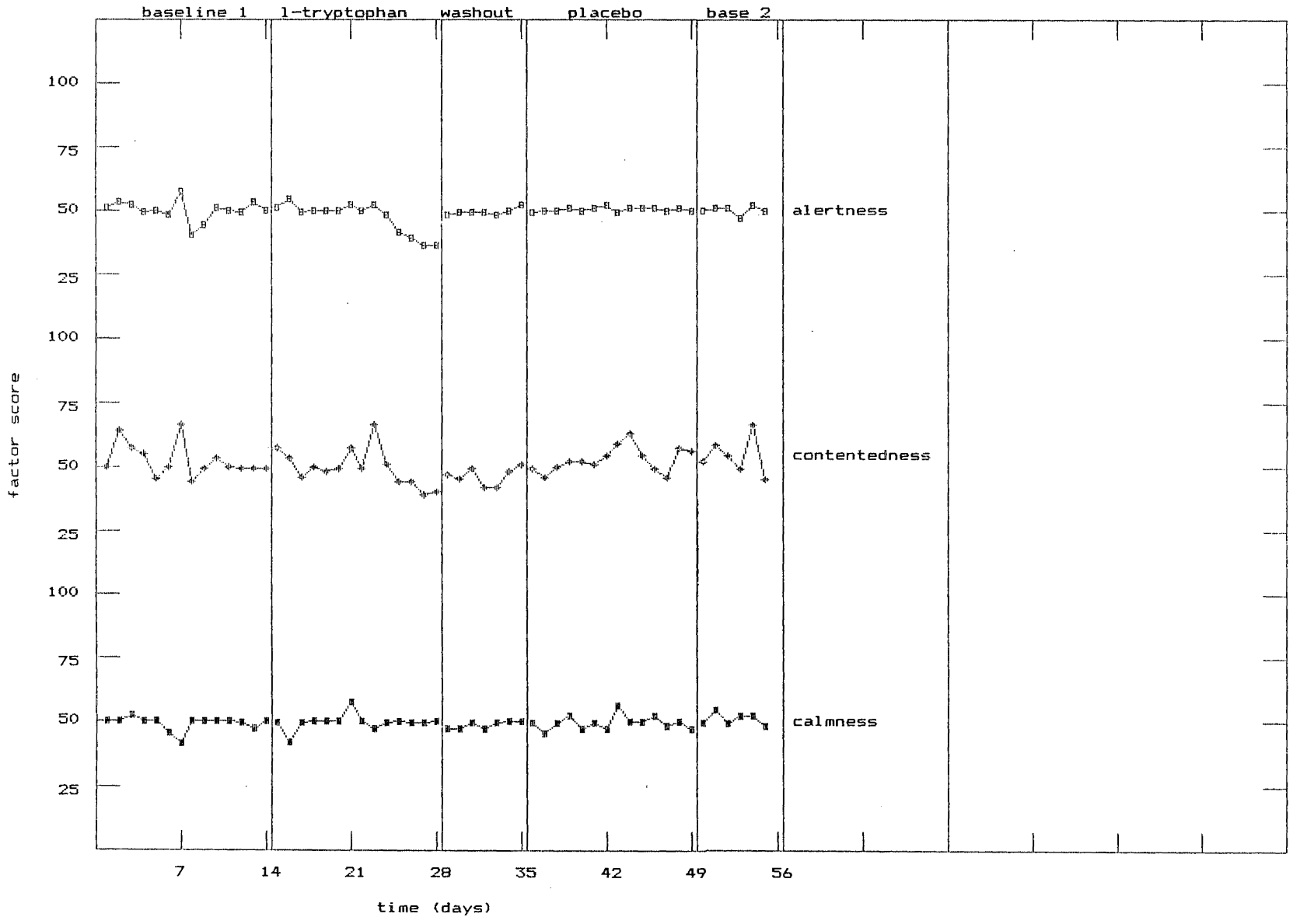


Figure 4-13-2
FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 13



Autocorrelation estimates

Table 4-12-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=13)			tryptophan(n=14)		
	r1	r2	r3	r1	r2	r3
alertness						
morning	-.39	-.16	.16	.64**	.39*	.003
evening	-.13	-.16	.06	.74**	.43*	.16
cont...ss						
morning	-.21	-.18	-.16	.21	-.12	-.06
evening	-.10	-.24	.09	.30	.15	-.06
calmness						
morning	.11	-.16	.04	-.05	-.60	.04
evening	.28	-.17	-.29	.12	-.16	-.02

Table 4-12-3 continued:

factor	placebo(n=14)		
	r1	r2	r3
alertness			
morning	-.03	.17	-.06
evening	-.23	.01	.09
cont...ss			
morning	-.13	-.33	.26
evening	.44*	-.19	-.35
calmness			
morning	.26	-.40	-.46
evening	-.18	.001	-.03

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Comment on t test results

As indicated in Table 4-13-4, the mean for morning contentedness in the tryptophan period was significantly below baseline and placebo phases. In addition, the level of morning alertness was found to be significantly lower during trytophan

phase relative to placebo. However, the reduction was not significant relative to baseline.

Table 4-13-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	~ 1.68 ns	-1.09 ns	~-2.38 *+
evening	1.41 ns	-1.73 ns	-2.05 ns
contentedness			
morning	~ 2.28 *	~-0.99 ns	~-2.80 *
evening	1.02 ns	-0.27 ns	-1.38 ns
calmness			
morning	0.22 ns	~ 1.31 ns	~ 1.26 ns
evening	-0.45 ns	-0.48 ns	0.00 ns

* exceeds critical value for the .05 level of significance

+ sig. t values affected by sig. levels of autocorrelation

- indicates the first mean of the pair is the lowest

C statistic results

Table 4-11-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	-1.49 ns	3.31 **
cont...ss	-0.60 ns	2.13 *
calmness	0.95 ns	0.80 ns
evening		
alertness	-0.49 ns	3.32 **
cont...ss	-0.35 ns	1.06 ns
calmness	1.18 ns	1.12 ns

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

Comment on C statistic results

As is evident from Table 4-11-5, for both morning and evening tryptophan phases, alertness and contentedness were found

to exhibit significant departures in trend relative to baseline.

(c) Hours of sleep

Table 4-13-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=13)			tryptophan(n=11)		placebo(n=13)		
r1	r2	r3	r1	r2	r1	r2	r3
.28	-.45	-.22	-.21	-.21	-.10	-.11	.05

None of the above estimates proved significant

t test value results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
0.67 ns	0.86 ns	0.12 ns

Comment on hours of sleep

As indicated from the t test results, no significant differences were apparent with respect to the mean hours of sleep between baseline tryptophan and placebo phases.

(d) Side effects

Table 4-13-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=14)			placebo(n=14)		
r1	r2	r3	r1	r2	r3	r1	r2	r3
-.20	-.11	.07	.77**	.50**	.23	-.10	-.11	-.12

** exceeds the critical value for the .01 level of significance

t test value results for side effect severity

base1 - tryp	base1 - plac	tryp - plac
~-1.57 ns	~ 1.41 ns	2.44 *

Comment on side effects

As indicated from the above t tests, although side effect severity was higher during the tryptophan phase relative to

placebo, the elevation was not significant with respect to baseline. An extreme elevation in the last four days of the tryptophan phase coincided with reports of flu over this period. Otherwise symptoms during the rest of the tryptophan period did not appear elevated, that is, the mean for the first 4 tryptophan days was 0.6 compared to 11.5 for the final 4 days. The presence of significant positive autocorrelation in the tryptophan phase may have resulted in an over-estimation of significance here.

(e) Premenstrual tension

The first menstrual onset for this subject was noted on day 6 of baseline 1 and the second on day 6 of the washout phase. The overlap of the second premenstrual phase with the last week of tryptophan intake as well as a flu attack makes it difficult to attribute symptom elevation to any one factor. However, elevation in side effects was confined the days of flu.

(5) Summary and Conclusions

The main findings for this subject were limited to slight elevation in weekly scale scores around the final week of tryptophan administration and during the washout phase. HSCL factor scores indicated most of the elevation was attributable to anxiety and somatic symptoms. This finding could be considered to coincide with the reduction in alertness and contentedness which was most apparent during the last four tryptophan days. This decline coincided severe flu symptoms over the period. The experience of flu might also account for the statistically significant reduction in the level of contentedness for the tryptophan phase relative to baseline and placebo and the significant departures in trend for tryptophan relative to baseline on both alertness and contentedness dimensions. The remaining statistically significant finding of reduced alertness in the morning (and increased side effects) for tryptophan relative to placebo was not maintained in relation to baseline. Thus, no significant changes in mood, total sleep time or side effects (relative to baseline and placebo periods) could be confidently associated with ingestion of 3gms/day of tryptophan for 14 days in this subjects.

4.2.14 Subject 14

(1) Demographic variables

age(yrs): 22 sex: male height(cms):185
weight(kgs):76.00
(within desirable weight range)
l-tryptophan experience: - not consumed prior to this project
motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial SDS score for this subject was close to the appropriate mean with respect to Knight et al.'s (1983) norms. Subsequent scores were close to or below this value. On this basis as well as a general interest motivation for participation the present subject was not considered to be depressed.

(b) Anxiety status

The Trait anxiety score for this subject (33) was well within one standard deviation from the appropriate mean according to Knight et al.'s (1983) norms. While the first baseline State score slightly exceeded one standard deviation above the mean, subsequent values were under this limit. Consequently this subject was not considered to be particularly anxious.

(3) Experimental variables

(a) Dose level(gms/day): 4

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	7days	7days	14days	7days

Mood ratings were not obtained for this subject during the washout phase. Originally this subject had intended completing

two weeks of tryptophan consumption. However, owing to a sudden requirement to leave Christchurch, data was not obtained for the second tryptophan week or the washout phase.

(c) Extra details

Scale completion time was regular and moodscale ratings were missed once. Weekly rating for mid baseline and the end of baseline 2 were missed. No tablets were forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-14-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan	wash	placebo	
day	01	07	14	21	28	35	42
scale							
zung	33	-	30	25	-	26	24
state	40	-	34	35	-	34	25
HSCL	68	-	71	74	-	75	65

Table 4-14-2 HSCL factor scores

	baseline 1			tryptophan	wash	placebo	
day	01	07	14	21	28	35	42
factor							
1	1.18	-	1.15	1.49	-	1.17	1.20
2	1.10	-	1.22	1.48	-	1.46	1.00
3	1.16	-	1.16	1.12	-	1.32	1.16
4	1.29	-	1.28	1.18	-	1.40	1.09
5	1.15	-	1.15	1.00	-	1.15	1.15

Comment on weekly scale scores

The consistency of low scores across all phases was confirmatory of the present subject's non depressed and non anxious status. HSCL factor scores were in keeping with means for a normal sample (see Table 3-4).

(b) Mood factors

Visual analysis of graphed data

No consistent or meaningful changes could be detected from the graphed morning and evening data for this subject in Figure 4-14. The brevity of the tryptophan period was a handicapp to valid analysis in this respect. The unusual events noted e.g. smoking of 6 marijuana joints on the second evening of baseline 1 were not associated with any dramatic or meaningful changes in mood ratings. However, it should be noted that the first mood scale completion following this event was not until the next morning. Similarly, consumption of two (unspecified) antidepressants on the evening prior to day 6 of the placebo phase was not associated with any outstanding changes in mood ratings.

Autocorrelation estimates

Table 4-14-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=7)	placebo(n=14)		
	r1	r2	r3	r1	r1	r2	r3
alertness							
morning	.13	.36	.07	-.02	-.30	-.19	.18
evening	.45*	.04	-.25	-.24	-.08	-.18	-.29
cont...ss							
morning	-.38	.12	-.28	.01	-.10	-.22	-.05
evening	-.38	.12	-.28	.40*	.49**	.37*	.20
calmness							
morning	.12	-.33	.22	.18	.10	.12	.23
evening	-.09	.10	.19	-.35	.27	.24	-.09

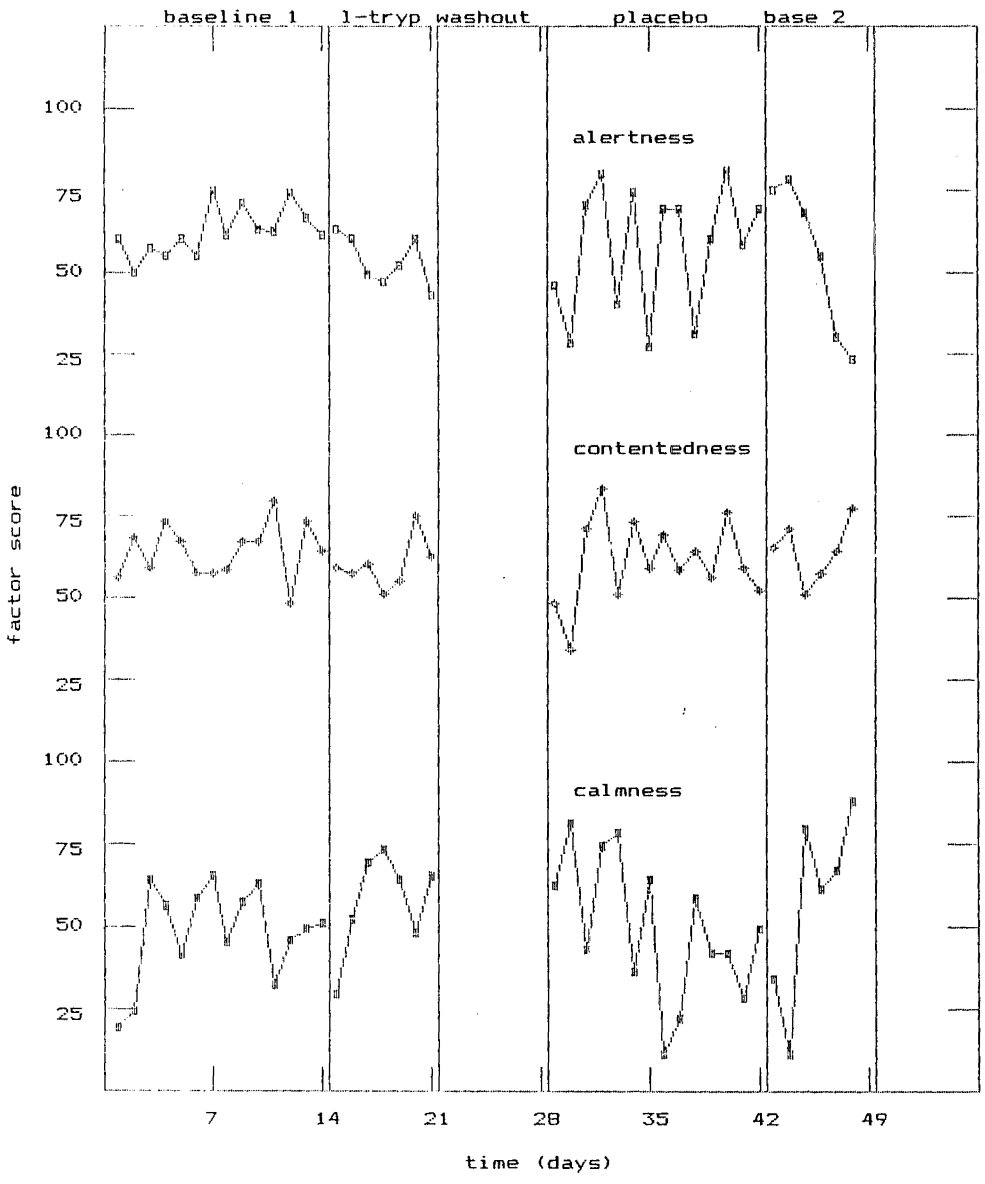
* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

Figure 4-14

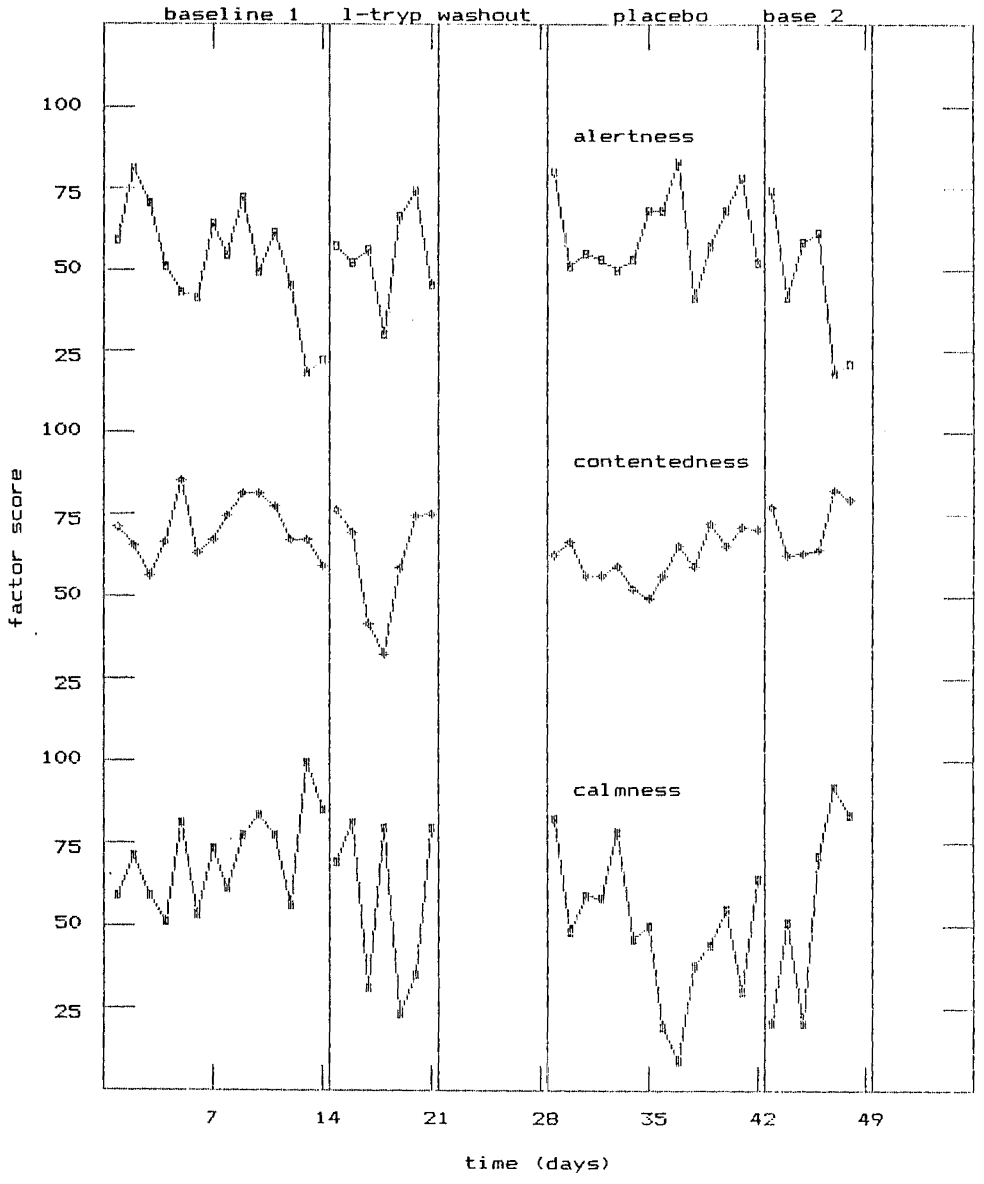
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 14



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 14



t test results

Table 4-14-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	tryp - plac	base1 - plac
alertness			
morning	2.55 *	~ 0.88 ns	~-0.65 ns
evening	-0.28 ns	-1.54 ns	-1.12 ns
contentedness			
morning	1.05 ns	0.70 ns	-0.20 ns
evening	~ 1.80 ns	2.89 **+	~-0.08 ns
calmness			
morning	-1.36 ns	-0.21 ns	0.87 ns
evening	~ 1.30 ns	3.28 **	0.80 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

\+ sig. t values affected by sig. levels of autocorrelation

\- indicates the first mean of the pair is the lowest

Comment on t statistic results

As evident from Table 4-12-4, the level of morning alertness was found to be significantly lower than baseline but not placebo for this subject. In addition, the level of evening contentedness and calmness was significantly lower for placebo relative to baseline. The significance of the placebo - baseline difference on contentedness may have been underestimated due to the presence of significant positive autocorrelation in both these phases.

(c) Hours of Sleep

Table 4-14-5 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=13)			tryptophan(n=7)	placebo(n=14)		
r1	r2	r3	r1	r1	r2	r3
.11	-.33	-.44	-.06	-.16	-.11	-.03

None of the above estimates proved significant

t test results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
-1.38 ns	0.02 ns	1.05 ns

Comment on hours of sleep

No significant differences in mean hours of sleep were apparent between baseline, tryptophan and placebo phases for this subject.

(d) Side effects

No side effects were checked by this subject throughout the total trial length.

(5) Summary and Conclusions

Both statistical and visual analysis, for this subject, were hindered by the brevity of the tryptophan phase. Consistently low scores on the weekly scales, were confirmatory of the lack of depressive and anxious symptomatology in the present subject. The statistically significant finding of reduced morning alertness for tryptophan relative to baseline in the morning series was not considered particularly relevant due to the shortness of this phase, the lack of difference relative to placebo and the absence of visual support. The significant reduction in calmness and contentedness for evening placebo relative to baseline phases was not supported by visual analysis.

Thus, consumption of 4gm/day of tryptophan for 7 days by the present subject could only be associated with a slight statistically significant reduction in alertness. No elevation in side effect severity was attributable to this treatment.

4.2.15 Subject 15

(1) Demographic variables

age(yrs): 20 sex: male height(cms):175

weight(kgs):83.00

(above desirable weight range)

tryptophan experience: - not consumed prior to this project

motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial SDS score for this subject was close to the appropriate mean for age and sex according to Knight et al.'s (1983) norms. Despite a general interest motivation for participation, most of the remaining scores were particularly elevated according to the above criteria. On the basis of Zung's (1972) depression categories, two scores were within the mild to moderate range and one fell within the moderate to severe class. While, some consideration was given to therapeutic relationships this subject was not considered in the depressive category.

(b) Anxiety status

The Trait score (42) for the present subject exceeded one standard deviation above the mean for Knight et al.'s (1983) norms. Initial State scores were close to the mean, while, four subsequent scores exceeded one standard deviation above the mean and one of these scores was in excess of three standard deviations above the mean. Thus, the present subject experienced elevated levels of anxiety on occasions.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo
14days	14days	7days	14days

(c) Extra details

Scale completion time was regular with some missing data accrued for the daily mood ratings. The final weekly scale ratings were missed. No tablets were forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-15-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
scale							
zung	33	35	40	38	37	43	50
state	32	34	58	38	41	36	29
HSCL	89	85	96	89	93	107	108

Table 4-15-2 HSCL factor scores

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
factor							
1	1.48	1.26	1.56	1.37	1.41	1.25	1.07
2	1.77	1.73	1.85	1.57	1.57	2.24	2.49
3	1.46	1.26	1.85	1.29	1.29	2.06	1.72
4	1.44	1.53	1.51	1.70	1.56	2.20	2.11
5	1.58	1.73	1.55	1.42	1.70	1.70	1.73

Comment on weekly scale scores

A rise in total scores for the Zung and HSCL scales was apparent during the washout and placebo phases. Most HSCL elevation was attributable to 'interpersonal sensitivity',

'depression' and 'obsessive-compulsive' factors. The elevated State score at the end of the baseline phase was associated with a notable rise on the HSCL factor of 'interpersonal sensitivity'. No changes in weekly ratings could be meaningfully related to tryptophan intake. HSCL factor scores 2 to 5 exhibited levels close to depressed and anxious groups at times (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

Morning and evening series (Figure 4-15) did not indicate any dramatic within or between phase changes. There was, however, a slight trend for reduced alertness in the morning and evening series during the tryptophan phase relative to baseline, with the indication being most consistent in the morning. The reductions were less pronounced relative to the erratic and broken placebo periods. Frequent consumption of alcohol by this subject did not bear any consistent relationship to mood ratings. Evening scales were generally completed prior to alcohol consumption at night, thus, only the morning after ratings could be considered. The peak during the evening placebo phase (day 42) for all dimensions coincided with an apparently enjoyable celebration.

Autocorrelation estimates

Table 4-15-3 rk (k=1,n/4) values for separate morn. & eve. series

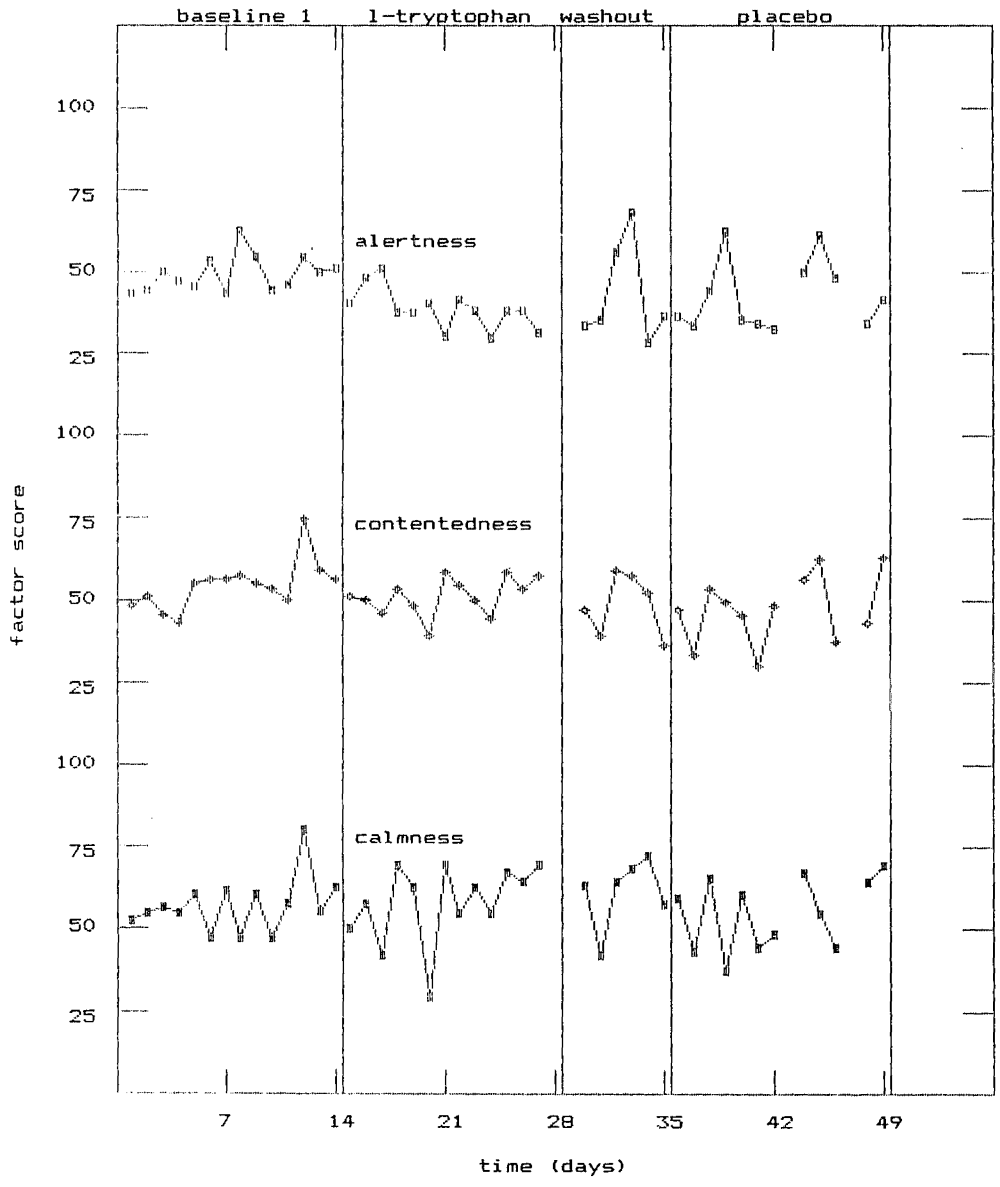
factor	baseline 1(n=14)			tryptophan(n=13)			placebo(n=14)		
	r1	r2	r3	r1	r2	r3	r1	r2	r3
alertness									
morning	-.10	-.15	.05	.19	-.02	.33	.17	-.54*	-.51*
evening	-.22	.28	-.27	-.11	-.08	-.24	.06	-.35	-.53*
cont...ss									
morning	.25	.08	-.03	-.15	-.20	.02	-.07	-.43	-.13
evening	.13	-.08	.01	-.45	.19	.03	-.06	-.34	-.41
calmness									
morning	-.23	.16	-.02	-.32	.03	.15	-.37	.03	.09
evening	.22	.05	.04	-.50*	.44*	-.05	.22	-.60*	-.43

* exceeds the critical value for the .05 level of significance

Figure 4-15

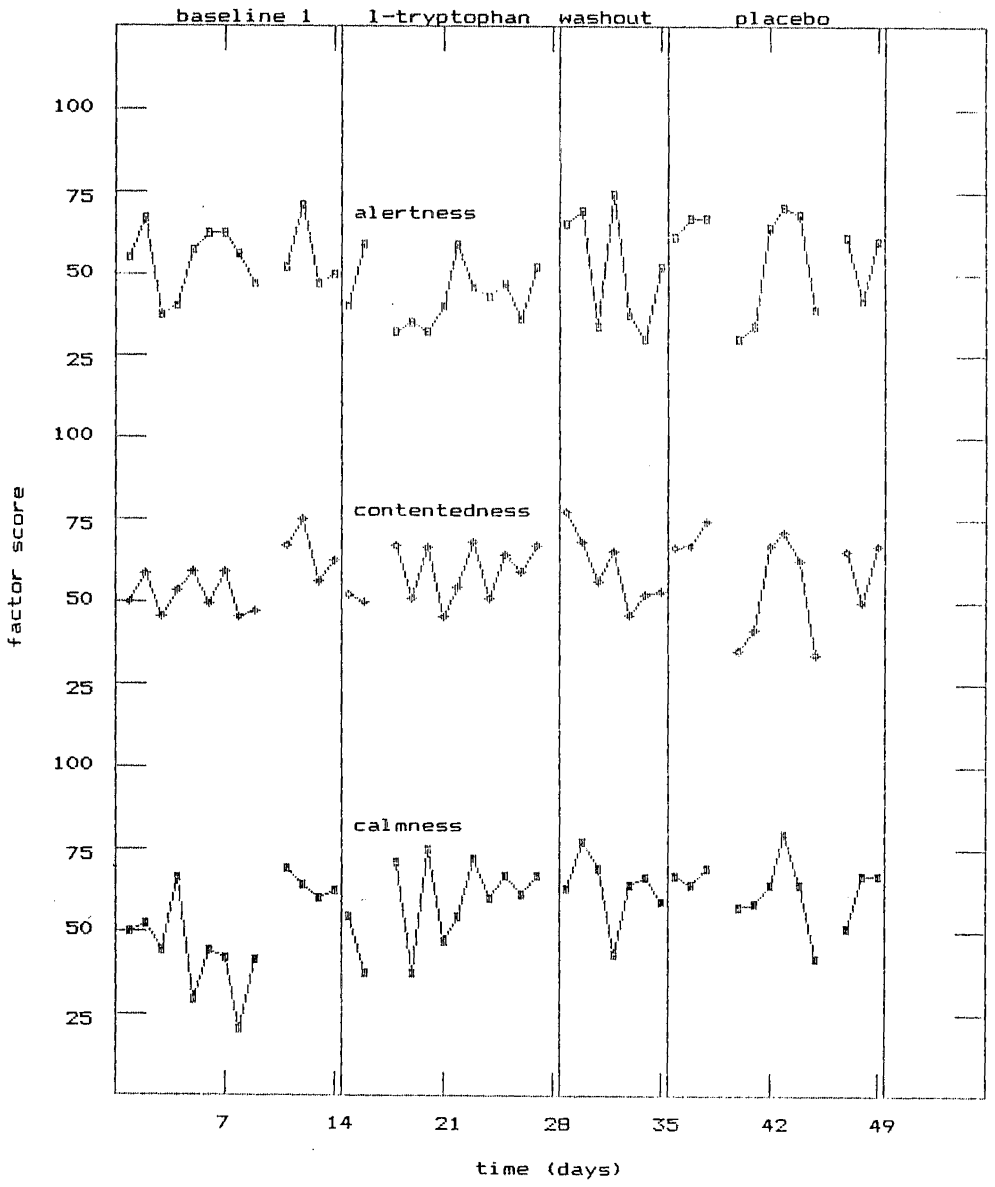
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 15



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 15



t test results

Table 4-15-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	4.70 **	~ 1.90 ns	~-1.21 ns
evening	2.73 *	-0.24 ns	~-2.35 *+
contentedness			
morning	1.30 ns	1.98 ns	~ 1.11 ns
evening	-0.60 ns	-0.53 ns	~-0.09 ns
calmness			
morning	-0.24 ns	0.54 ns	0.67 ns
evening	-1.96 ns	-2.59 *+	-0.84 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

\+ sig. t values affected by sig. levels of autocorrelation

\- indicates the first mean of the pair is the lowest

Comment on t test results

As is evident from Table 4-15-4, the level of alertness was found to be significantly reduced relative to baseline in morning and evening series. For the evening series, tryptophan alertness was also found to be significantly lower than placebo, although the significance in this case may have been overestimated due to the presence of negative autocorrelation in the placebo phase. The other significant finding was for increased calmness for placebo relative to baseline in the evening.

C statistic results

Comment on C statistic results

As indicated in Table 4-15-5, the trend in mood ratings for morning alertness during the tryptophan phase was shown to depart significantly from baseline.

Table 4-15-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	-0.21 ns	2.66 **
cont...ss	1.14 ns	1.03 ns
calmness	-0.83 ns	-1.43 ns
evening		
alertness	-0.08 ns	1.03 ns
cont...ss	0.65 ns	-0.42 ns
calmness	0.99 ns	0.28 ns

** exceeds the critical value for the .01 level of significance

(c) Hours of sleep

Table 4-15-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=11)		tryptophan(n=13)			placebo(n=12)		
r1	r2	r1	r2	r3	r1	r2	r3
.12	-.22	-.42	.20	-.22	.18	.27	-.16

None of the above estimates proved significant

t test results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
-2.22 *	~-0.04 ns	1.80 ns

Comment on hours of sleep

The mean hours of sleep were significantly higher for the tryptophan phase relative to baseline but not placebo.

(d) Side effects

Table 4-15-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=13)			tryptophan(n=12)			placebo(n=12)		
r1	r2	r3	r1	r2	r3	r1	r2	r3
.47	.01	-.25	-.18	.06	.01	.04	-.13	.33

None of the above estimates proved significant

t test results for hours of side effect severity

base1 - tryp	base1 - plac	tryp - plac
-0.57 ns	1.06 ns	1.66 ns

Comment on side effects

As is evident from the above t test results, no significant changes in symptom severity were apparent between baseline, tryptophan and placebo phases for this subject. Examintation of the types of symptoms reported throughout the trial indicated no obvious between phase differences.

(5) Summary and Conclusions

The main feature which could be quite confidently associated with tryptophan intake in this subject was the reduction in the level of alertness for tryptophan relative to baseline in both series. This finding was corroborated by both visual and statistical analysis. A reduction in slope for tryptophan relative to baseline in the morning, was supported by the C statistic application in this case. A significant t test, indicating the level of tryptophan alertness to be below placebo in the evening, was not supported visually. The second main finding of increased sleep time during the tryptophan phase relative to baseline could be considered in keeping with the reduction in alertness. Although the above changes associated with tryptophan intake were not maintained relative to placebo, they were still considered to be potentially meaningful. Factors such as increased drowsiness emerge as one of the most common effects associated with tryptophan intake in past investigations of normal subjects.

Thus, there were no indications of any therapeutic benefits in the present subject or changes relating to elevation of side effects following consumption of 3gms/day of tryptophan. Although there was consistent demonstration of reduced alertness for tryptophan relative to baseline periods, the reduction was only slight.

4.2.16 Subject 16

(1) Demographic variables

age(yrs): 39 sex: male height(cms):179
weight(kgs):70.00
(within desirable weight range)

drug consumption: antidepressant (mianserin: 60mg/day) was consumed prior to the tryptophan phase for comparison.

tryptophan experience: - not consumed prior to this project
motivation for participation: - depression

(2) Psychological variables

(a) Depression status

The inital and most subsequent SDS scores for this subject were in excess of 3 standard deviations above the mean according to Knight et al.'s (1983) norms. According to Zung's (1972) depression categories five out of six SDS scores for this subject were within the moderate to severe class with the sixth score just reaching the severe class. Thus, in combination with the motivation for participation, this subject was classed as depressed. In addition, it should be noted that the present subject was consuming therapeutic doses of mianserin on entry to the study and had been referred to the project from Student Health at Canterbury University.

(b) Anxiety status

The Trait score (62) for the present subject exceeded three standard deviations above the mean according to Knight et al.'s (1983) norms. The initial and all subsequent State scores exceeded 4 standard deviations above the mean. Thus, the present subject was considered to be experiencing extremely high levels of anxiety relative to a normal population (Knight et al., 1983).

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

mianserin	washout	tryptophan
10days	14 days	26days

(c) Extra details

Since the present subject was consuming mianserin at the time of inquirng about the project it was decided to collect mood data under this condition for comparison with tryptophan. The subject had been taking mianserin (60mg/day) for 4 weeks prior to the commencement of data collection. Scale completion time was regular. While several mood ratings were missed during the mianserin period the data for the tryptophan phase are relatively complete.

(4) Results and analysis:

(a) Weekly scores

Table 4-16-1
Total scores for Zung, State anxiety and HSCL scales

	mianserin			tryptophan		
day	01	07	14	21	28	35
scale						
zung	53	50	50	47	51	56
state	66	62	62	59	67	65
HSCL	114	144	127	133	130	138

Table 4-16-2
HSCL factor scores

	mianserin			tryptophan		
day	01	07	14	21	28	35
factor						
1	1.75	2.26	1.98	2.04	2.08	2.23
2	2.49	2.60	2.33	2.34	2.33	2.43
3	2.03	2.75	2.14	2.59	2.46	2.69
4	2.39	2.71	2.64	2.36	2.44	2.64
5	2.02	2.58	2.34	2.44	2.30	2.30

Comment on weekly scale scores

Total Zung, State anxiety and HSCL scores maintained an elevated level for the present subject across both mianserin and tryptophan phases. A two week washout period intervened between mianserin and tryptophan phases. However, data could not be obtained for this period. HSCL factor scores were in keeping with means for a depressed group (Table 3-4).

(b) Mood factors

Visual analysis of graphed data

The high incidence of missing data during the mianserin phase made comparison of drug conditions inappropriate. Although not evident from the graphs in Figure 4-16, a two week washout period intervened between mianserin and tryptophan periods. No trends were apparent to the present author for any dimension in either series. Morning and evening series showed similarity in the magnitude and direction of ratings.

Autocorrelation estimates

Calculations were omitted for the mianserin period due to the brevity and brokeness of this phase.

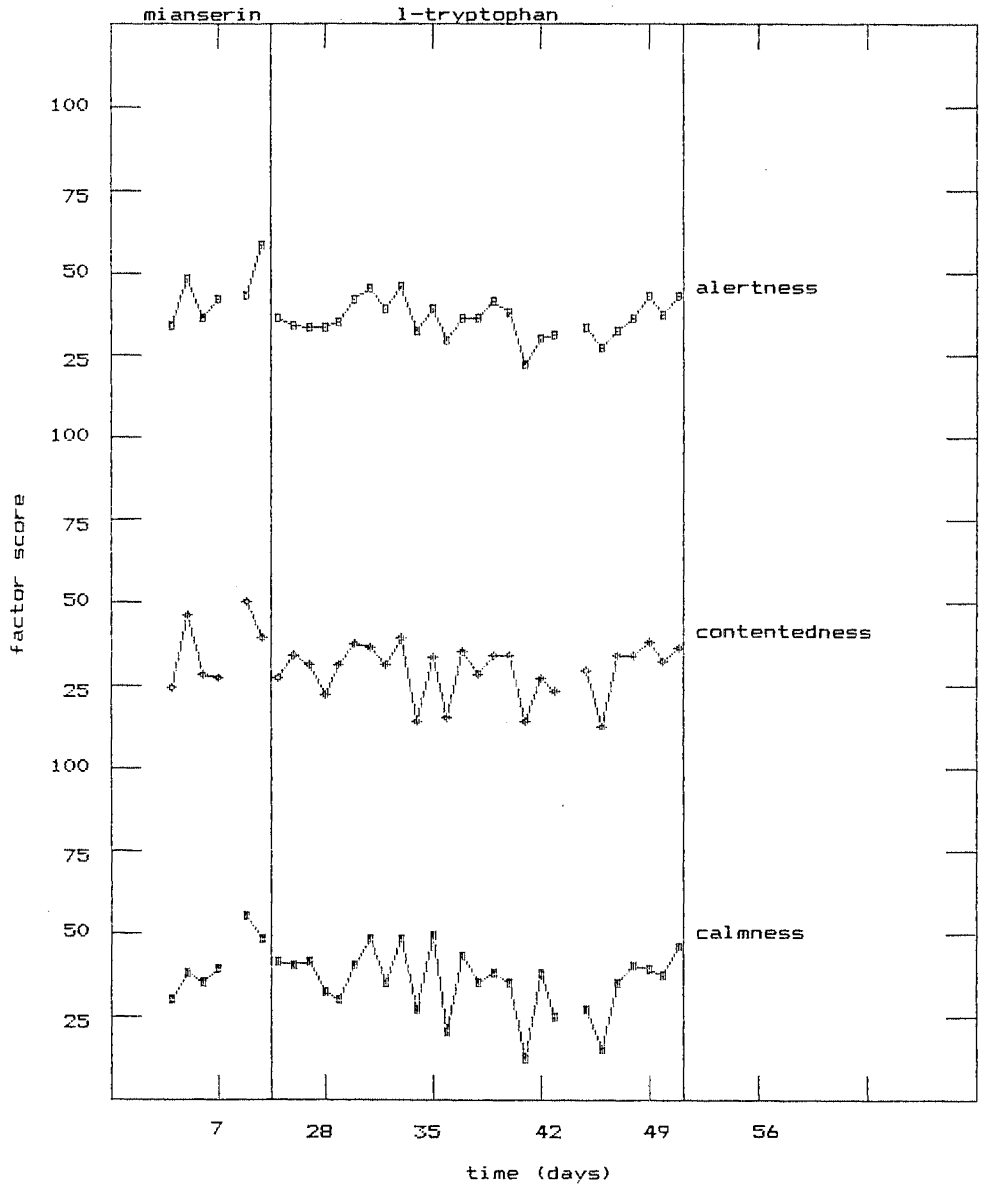
Table 4-16-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	tryptophan(n=26)			
	r1	r2	r3	r4
alertness				
morning	.29*	.27	-.14	-.02
evening	.34*	-.08	-.04	-.10
cont...ss				
morning	-.16	.28*	-.27	.03
evening	.26	-.03	-.35	-.27
calmness				
morning	-.11	.35*	-.14	.18
evening	.22	.07	.07	.07

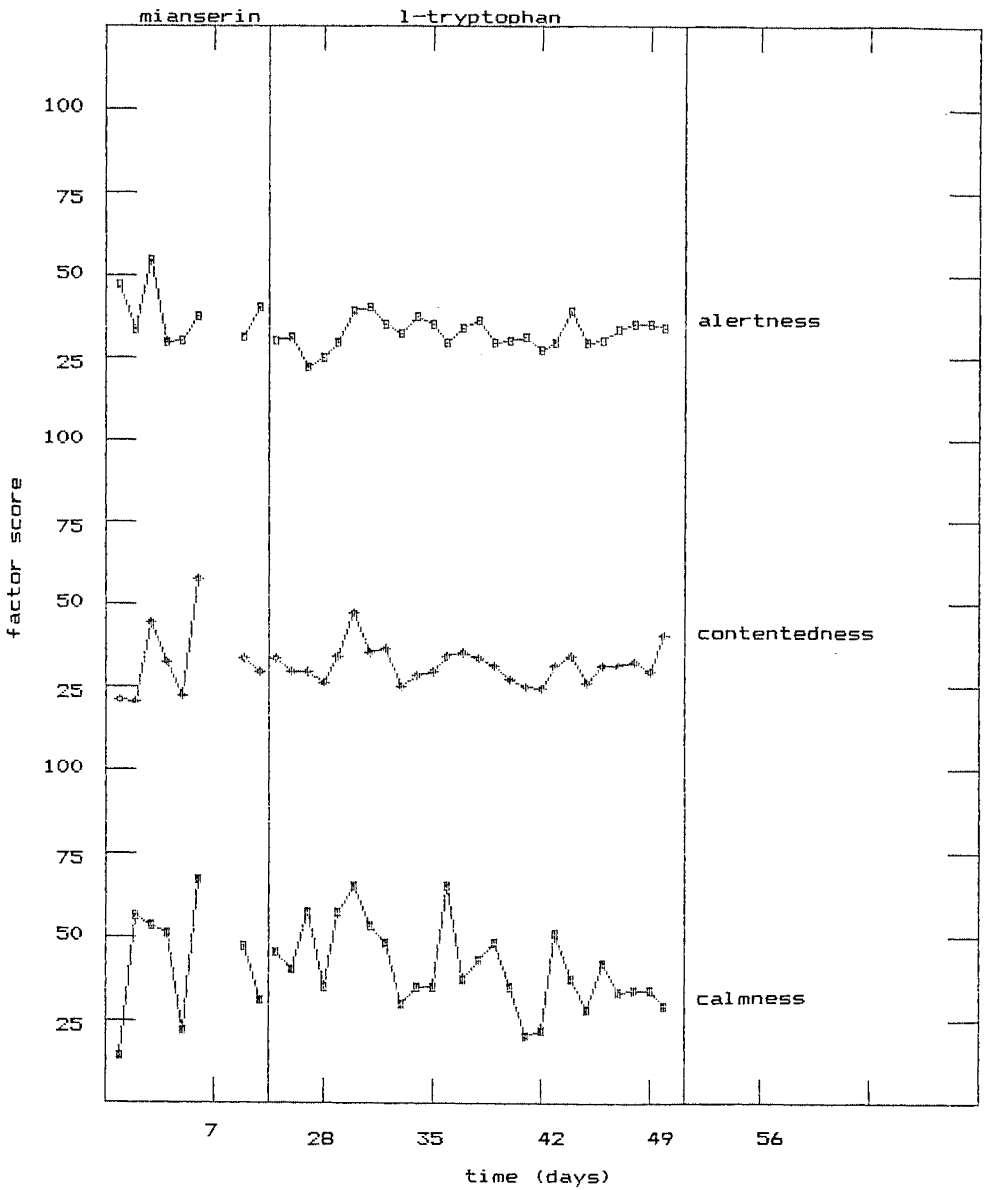
* exceeds the critical value for the .05 level of significance

Figure 4-16

FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 16



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 16



t test results

Owing to the brevity an frequency of missing data during the mianserin phase t-test comparisons could not be justified.

C statistic results

C statistic analysis was limited to the tryptophan period due to the brevity of the mianserin phase.

Table 4-16-4 Z values for morning and evening series

series	tryptophan
morning	
alertness	1.70 *
cont...ss	-0.79 ns
calmness	-0.41 ns
evening	
alertness	1.87 *
cont...ss	1.71 *
calmness	1.31 ns

* exceeds the critical value for the .05 level of significance

Comment on C statistic results

Statistically significant trends were detected for alertness in the morning and evening and for contentedness in the evening during the tryptophan phase.

(c) Hours of sleep

C-statistic result (Z value)

tryptophan
0.40 ns

Comment on hours of sleep

No significant trend, following C statistic application, was apparent for hours of sleep during the tryptophan phase.

(d) Side effects

C-statistic result (Z value)

tryptophan
0.09 ns

Comment on side effects

No significant trends with respect to side effect severity were apparent within the tryptophan phase as indicated by the C statistic.

(5) Summary and Conclusions

The moderately high levels of depression and quite extreme elevation of anxiety symptoms were maintained across both phases. Thus, there was no indication of therapeutic effects associated with tryptophan intake on the basis of these scales.

The brevity of the mianserin phase and the frequency of missing data during this period hindered valid visual or statistical comparison the two conditions. There was no indication from the graphed data that tryptophan administration was therapeutically superior to mianserin. While there was detection of statistically significant trends within the tryptophan phase for morning alertness and evening alertness and contentedness they were only slight and could not be confirmed as being particularly meaningful through visual inspection.

It is difficult to make a valid judgement concerning tryptophan's antidepressant and anxiolytic potential given the absence of baseline and placebo phases for comparison. Owing to the severity of symptoms in this case, it was not considered justifiable to subject this individual to non therapeutic conditions. There was no obvious increase in side effects throughout the tryptophan period. Thus, after a fair trial period of 26 days, tryptophan was unsucessful in reducing anxiety and depression scores to acceptable levels from the subject's view point or relative to Knight et al.'s (1983) anxiety and

depression scale norms.

Finally, it should be noted that this subject claimed to have obtained no therapeutic benefit from mianserin following, at least, a five week trial. There are claims that mianserin possesses antidepressant as well as antianxiety activity (Duquesne & Reeves, 1982). In addition, the subject claimed to have obtained little benefit from tricyclic compounds such as imipramine in the past. Thus, it could be speculated that the present subject was characterized by resistence to some forms of antidepressant medication.

4.2.17 Subject 17

(1) Demographic variables

age(yrs): 24 sex: male height(cms):160
weight(kgs):60.00
(within desirable weight range)
tryptophan experience: - not consumed prior to this project
motivation for participation: - depression

(2) Psychological variables

(a) Depression status

The initial and subsequent SDS scores for the present subject were all within one standard deviation from the mean according to Knight et al.'s (1983) norms. On this basis the present subject could not be considered depressed. However, this subject had been prescribed antidepressants in the recent past. In addition a motivation of depression for participation led to investigation of tryptophan's therapeutic potential in this case.

(b) Anxiety status

The Trait score (36) for this subject and the State anxiety scores throughout the trial were all within one standard deviation of the mean according to Knight et al.'s (1983) norms. On this basis the present subject was considered to be relatively free from anxiety symptoms.

(3) Experimental variables

(a) Dose level(gms/day): 4

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	21days	7days	14days	7days

(c) Extra details

A washout period of 7 days intervened between the second tryptophan period and the placebo phase, although data were not obtained for this time. Scale completion time was regular with a relatively low level of missing data. Weekly scale ratings were missed at the end of the second tryptophan and second baseline weeks. No tablets were forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-17-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan			wash	tryp2	placebo	
day	01	07	14	21	28	35	42	49	56	63
scale										
zung	33	35	37	31	30	30	35	-	33	36
state	31	36	31	32	26	33	34	-	32	39
HSCL	68	71	72	64	62	66	67	-	66	67

Table 14-17-2 HSCL factor scores

	baseline 1			tryptophan			wash	tryp2	placebo	
day	01	07	14	21	28	35	42	49	56	63
factor										
1	1.15	1.08	1.30	1.30	1.16	1.16	1.00	-	1.00	1.08
2	1.00	1.00	1.12	1.00	1.00	1.00	1.10	-	1.00	1.12
3	1.00	1.50	1.34	1.16	1.33	1.33	1.51	-	1.00	1.00
4	1.44	1.37	1.46	1.09	1.09	1.18	1.26	-	1.56	1.71
5	1.00	1.00	1.13	1.00	1.00	1.00	1.00	-	1.16	1.00

Comment on weekly scale scores

Low total scores on the Zung, State and HSCL scales were maintained across the total trial. Although a slight decline in scores was noted at week two of tryptophan ingestion, it was not considered sufficient to be of psychological significance. HSCL factor scores were in keeping with means from a normal group (Table 3-4) throughout the trial.

(b) Mood factors

Visual analysis of graphed data

The main between phase comparisons for this subject concerned baseline 1, the first tryptophan period and the placebo phase. No noticeable changes between or within such phases were apparent for the morning or evening series (Figures 4-17-1 and 4-17-2). The second tryptophan period did not exhibit any consistent parallels with the start of the first tryptophan phase.

Figure 4-17-1
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA
SUBJECT: 17

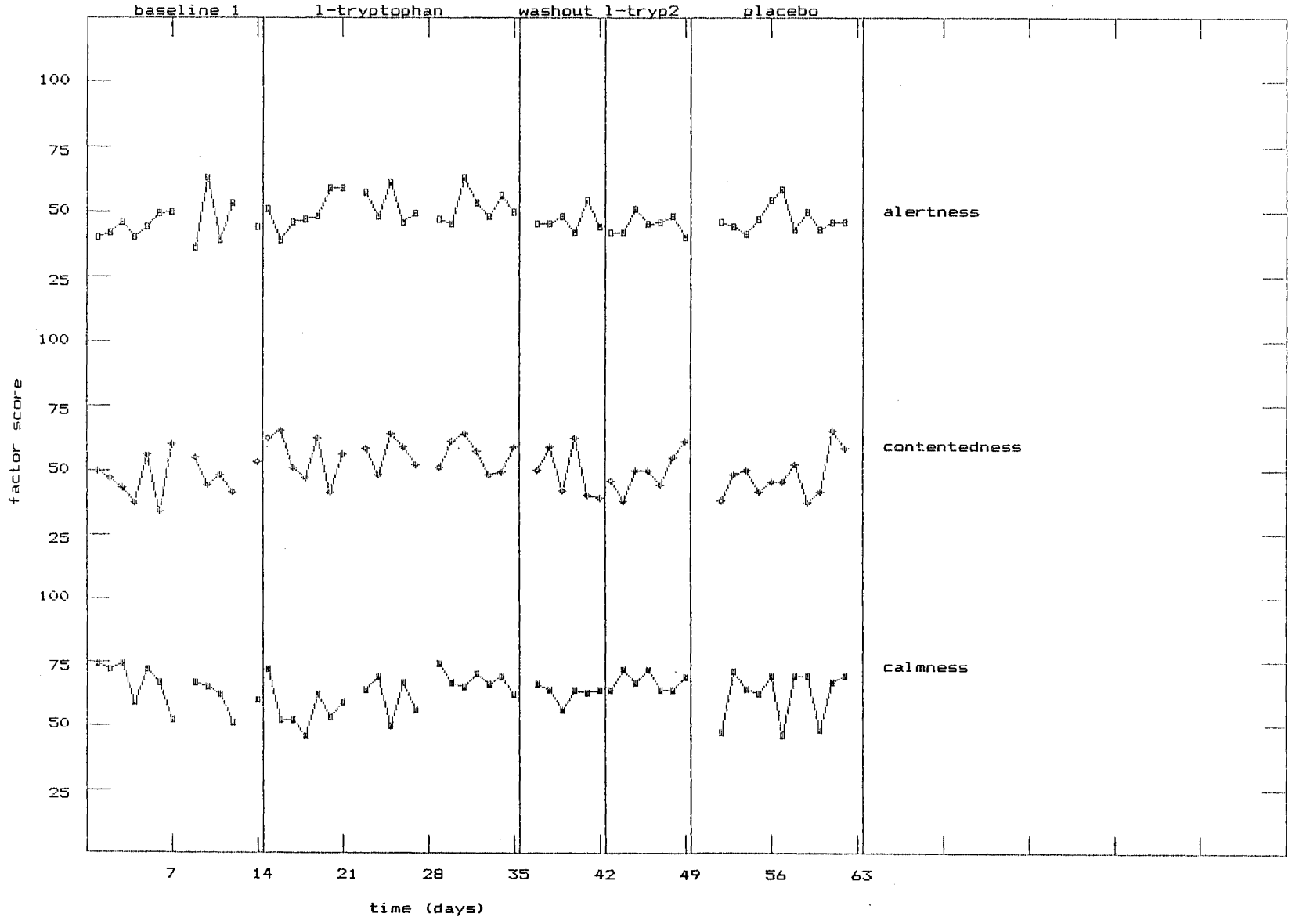
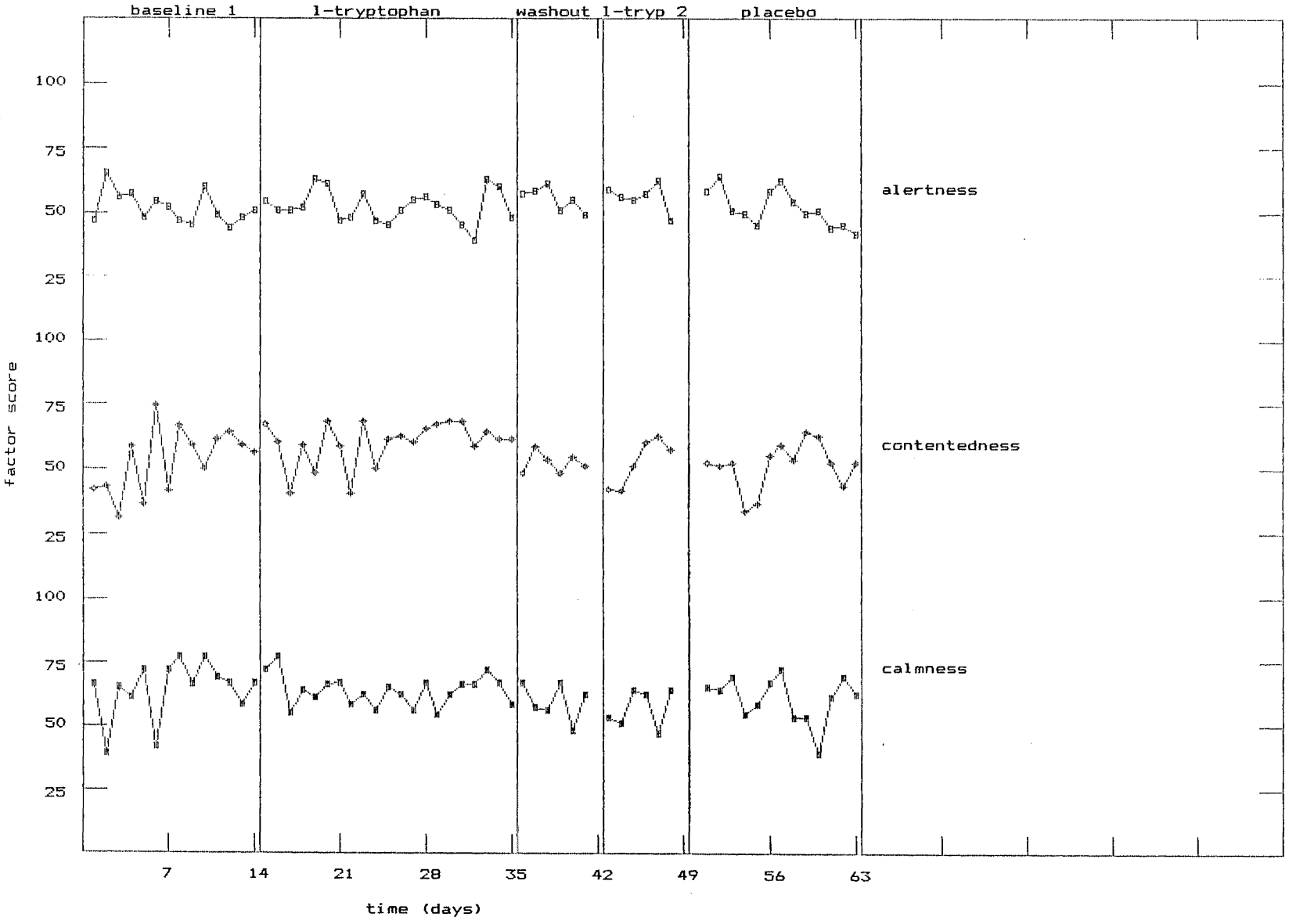


Figure 4-17-2
FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA
SUBJECT: 17



Autocorrelation estimates

Table 4-17-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=21)			
	r1	r2	r3	r1	r2	r3	r4
alertness							
morning	-.58*	.39*	-.06	.07	.05	.01	-.37
evening	-.01	-.08	-.05	.11	-.48*	-.09	.02
cont...ss							
morning	-.43	.13	-.08	-.11	-.29	.10	-.19
evening	-.21	.55**	-.14	-.11	.17	.16	-.16
calmness							
morning	.14	.02	.16	.09	.35	-.07	.20
evening	-.15	.08	-.05	-.02	-.02	-.02	-.22

Table 4-17-3 continued:

factor	placebo(n=14)		
	r1	r2	r3
alertness			
morning	.13	-.06	-
evening	.42*	-.02	-.25
cont...ss			
morning	.11	-.39	-
evening	.41	-.15	-.14
calmness			
morning	-.43	-.24	-
evening	.21	-.24	-.45

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Comment on t test results

The mean for morning alertness was significantly lower during baseline than tryptophan. The tryptophan phase exhibited significantly higher levels than either baseline or placebo for morning contentedness and the evening tryptophan period was higher relative to placebo for this dimension (Table 4-17-4).

Table 4-17-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	-2.26 *+	-0.59 ns	1.81 ns
evening	-0.28 ns	-0.08 ns	0.17 ns
contentedness			
morning	-3.01 **	0.02 ns	2.85 **
evening	-1.92 ns	0.42 ns	2.79 **
calmness			
morning	0.92 ns	0.72 ns	-0.02 ns
evening	~ 0.20 ns	0.93 ns	~ 1.17 ns

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

\+ sig. t values affected by sig. levels of autocorrelation

\- indicates the first mean of the pair is the lowest

C statistic results

Table 4-17-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	-2.01 *	~-2.37 **
cont...ss	-1.54 ns	0.27 ns
calmness	0.84 ns	0.87 ns
evening		
alertness	0.04 ns	0.50 ns
cont...ss	-0.70 ns	-0.25 ns
calmness	-0.60 ns	-0.56 ns

** exceeds the critical value for the .01 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see Chapter III for explanation)

Comment on C statistic results

As indicated in Table 4-17-4, there was a signifcant departure for the first tryptophan period relative to baseline. However, due to the presence of a significant trend in the

baseline 1 phase, the baseline - tryptophan comparison only involved the 12 tryptophan days. As indicated in figure 4-17-1, the first part of the tryptophan phase for alertness was associated with an increasing trend which was not characteristic for the entire phase.

(c) Hours of sleep

Table 4-17-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=10)		tryptophan(n=18)				placebo(n=10)	
r1	r2	r1	r2	r3	r4	r1	r2
-.26	-.12	.05	.18	.43**	.11	-.13	-.21

t test value results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
-0.64 ns	~ 1.71 ns	2.24 *+

Comment on hours of sleep

As indicated from the above t test results, the mean hours of sleep was significantly greater for this subject during the tryptophan phase relative to placebo, however, the difference was not significant relative to baseline. The presence of signifcant positive levels of autocorrelation in the tryptophan period may have led to an underestimation of significance for the tryptophan - placebo difference.

(d) Side effects

A very low incidence of side effects was noted for this subject throughout the trial period. Only two headaches were reported during the baseline and first tryptophan periods. Thus, there was no indication of increasing side effect severity assocaited with either tryptophan phase.

(5) Summary and Conclusions

Despite the present subject's stated motivation for participation of depression, SDS scores were not supportive of this status, either at entry to the trial or at later stages of the program. The main statistical finding of increased morning contentedness for the tryptophan period relative to baseline and placebo phases was mildly corroborated following visual analysis. However only a few scores could be considered particularly elevated in this phase.

The other statistical finding of a significant increase in the alertness level for the tryptophan phase relative to baseline was in part supported by the significant C statistic outcome indicating that the tryptophan ratings departed in trend from baseline. However, as mentioned previously, the C statistic application only involved the first 12 points of the tryptophan phase. As is evident from visual appraisal, the increasing trend for this section could not reasonably be generalized to the remainder of the phase and the change in level for the tryptophan phase was not maintained relative to the placebo. An increase in total sleep time during the tryptophan phase was significant relative to placebo but not to baseline. Finally there was no evidence for increased severity and qualitative changes with respect to side effects associated with either tryptophan period for the present subject.

At completion of the trial the present subject claimed to have felt much better during the first and second periods of tryptophan intake but not during the placebo phase. While an increase in contentedness was indicated statistically (and to a slight extent visually), it may be that the scales employed in the present study were irrelevant or insenstive to the kind of depression the present subject claimed to experience and obtain relief from.

4.2.18 Subject 18

(1) Demographic variables

age(yrs): 22 sex: female height(cms):162
weight(kgs):59.00
(within desirable weight range)
tryptophan experience: - not consumed prior to this project
motivation for participation: - depression

(2) Psychological variables

(a) Depression status

The initial SDS score as well as most subsequent totals exceeded 2 standard deviations above the mean according to Knight et al.'s (1983) norms. Five of the seven ratings obtained throughout the trial for this subject were within the range appropriate to Zung's (1972) category of moderate to severe depression. This information together with a motivation of depression for participation led to placement of this subject within the depressed category.

(b) Anxiety status

The Trait anxiety score for the present subject (62) was approximately 3 standard deviations above the mean according to Knight et al.'s (1983) norms. The initial State score, however, was below the mean and most subsequent ratings were within one standard deviation above this mean. Although the Trait score may indicate a tendency towards experiencing high State anxiety in certain circumstances, this potential was not realized during the present study. This subject only exhibited significant elevation in anxiety on one occasion during the experiment.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo	baseline 2
14days	14days	7days	7days	7days

(c) Extra details

Scale completion time was regular and weekly scales were missed at the end of the second baseline week, while only two morning mood ratings were missed. No tablets were forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-18-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
scale							
zung	50	51	49	49	39	48	39
state	29	35	36	41	36	54	41
HSCL	124	107	114	113	101	115	91

Table 4-18-2 HSCL factor scores

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
factor							
1	2.15	1.98	1.73	1.72	1.76	1.97	1.70
2	2.36	1.65	1.67	2.13	1.91	1.99	1.69
3	2.09	1.91	2.37	1.62	1.85	1.85	1.61
4	1.76	1.93	2.47	2.88	1.95	2.47	1.77
5	2.61	1.59	1.77	1.62	1.75	2.04	1.31

Comment on weekly scale scores

As is apparent from Table 4-18-1, Zung total scores were maintained at a high level throughout the trial period. The limitation of single scores for the placebo phase hindered

comparison of this period with tryptophan and baseline phases. There was a slight reduction in Zung scores for the tryptophan phase relative to baseline. However, the reduction was also apparent during the placebo phase. The week of the highest State anxiety rating i.e. at the end of the washout phase coincided with reported nervousness relating to exams the following week. No clear patterns of changing factor scores for the HSCL scale could be determined between phases.

(b) Mood factors

Visual analysis of graphed data

Both morning and evening graphed data for this subject appear in Figure 4-18. High day to day variability was apparent for both series, across all phases. No consistent trends or changes in level between or within phases could be detected by the author. Reporting of unusual events such as nervousness relating to impending exams were not marked by any obvious changes in graphed mood ratings.

Autocorrelation estimates

Table 4-18-3 rk (k=1,n/4) values for separate morn. & eve. series

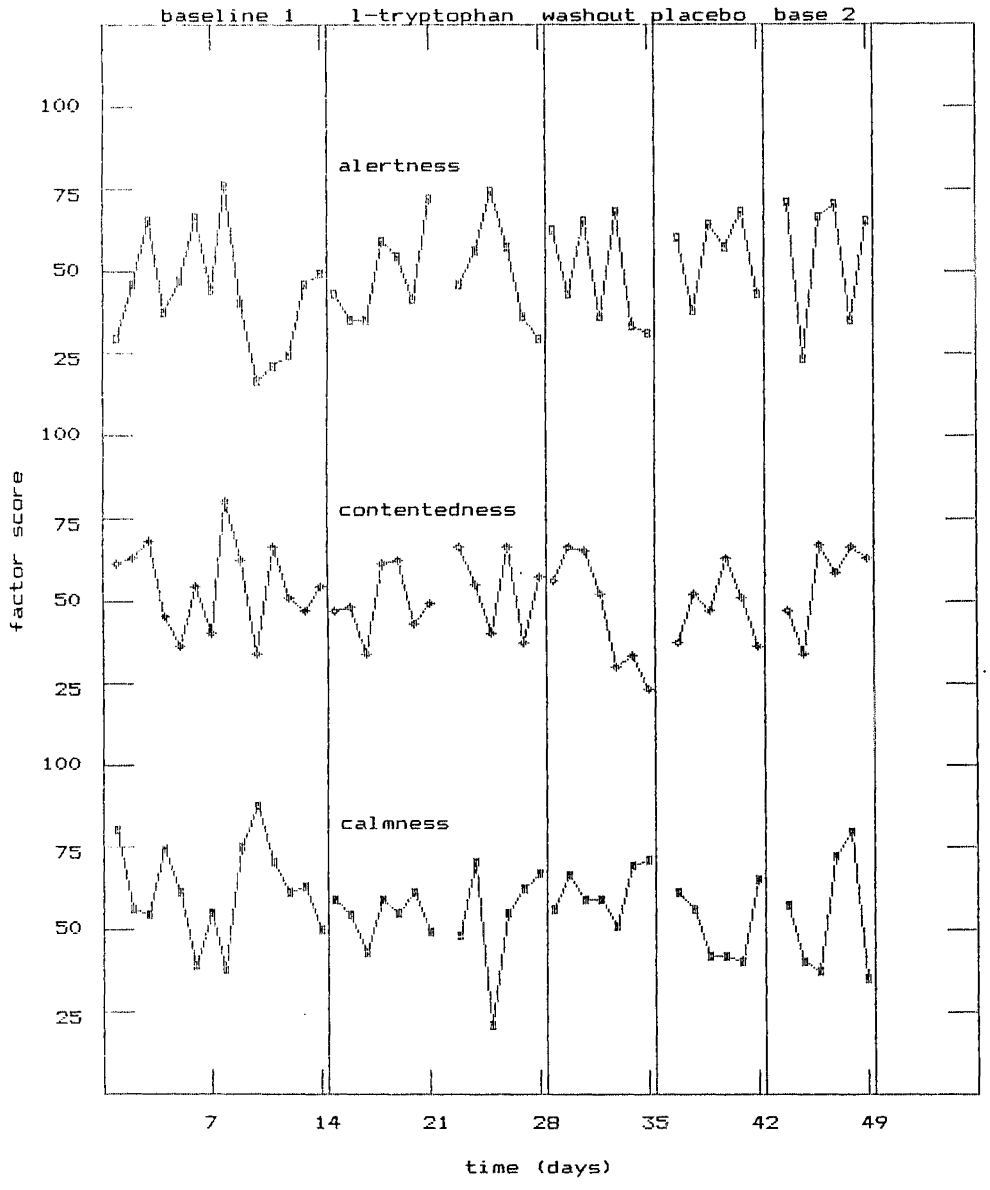
factor	baseline 1(n=14)			tryptophan(n=14)			placebo(n=7)
	r1	r2	r3	r1	r2	r3	r1
alertness							
morning	.24	-.03	-.06	-.003	-.14	.32	-.49
evening	.24	-.03	-.06	.07	-.01	-.02	-.04
cont...ss							
morning	-.15	-.24	.06	-.38	-.17	.21	-.09
evening	.23	-.19	-.07	.07	-.01	-.02	-.07
calmness							
morning	.14	-.19	-.15	-.32	-.10	-.06	.05
evening	.08	.26	-.27	-.17	.18	-.26	-.32

None of the above calculations proved to be significant

Figure 4-18

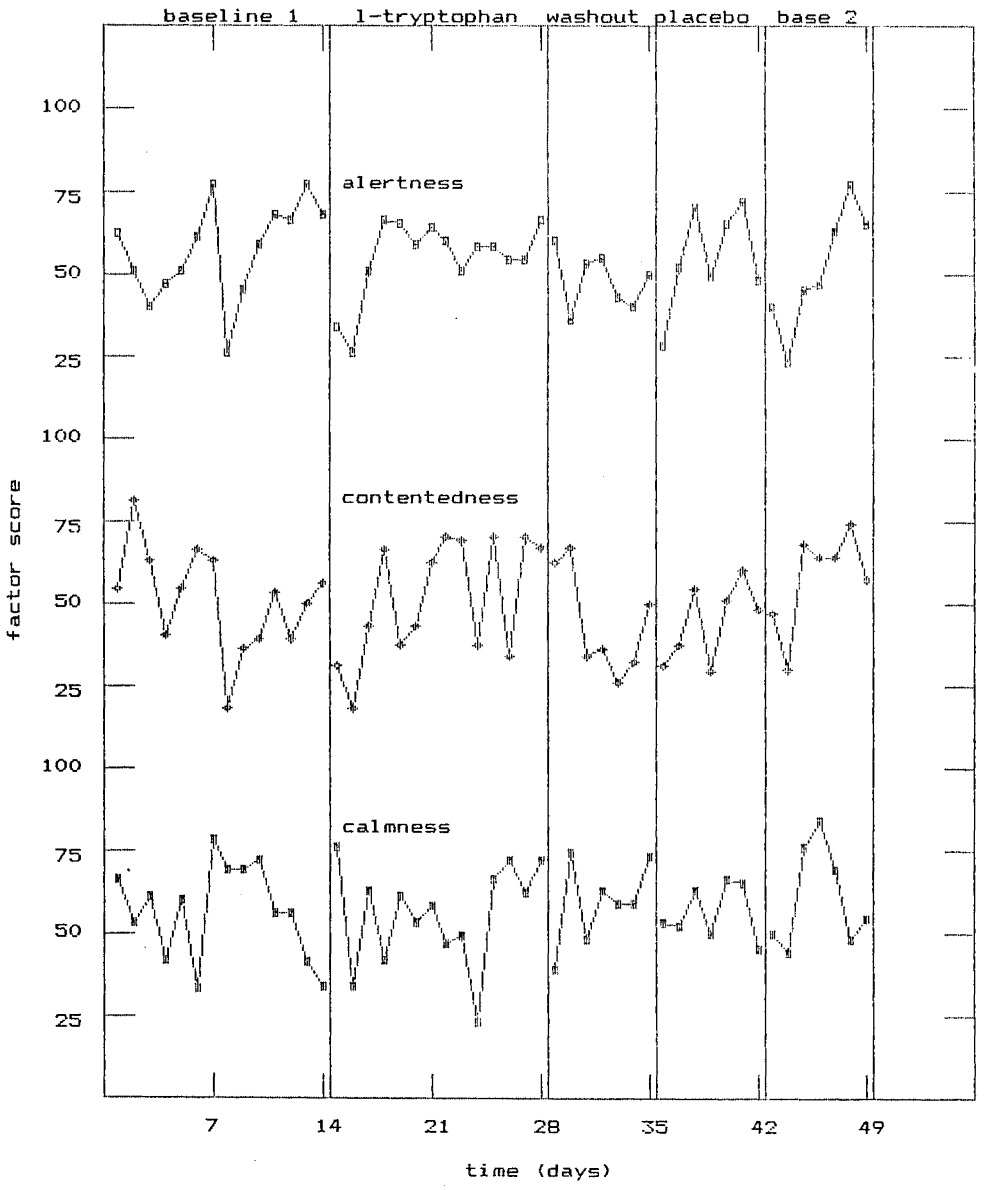
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 18



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 18



t test results

Table 4-18-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	-1.33 ns	-1.49 ns	-0.60 ns
evening	0.93 ns	0.31 ns	-0.45 ns
contentedness			
morning	0.62 ns	1.10 ns	0.59 ns
evening	-0.06 ns	0.97 ns	0.91 ns
calmness			
morning	1.45 ns	1.60 ns	0.52 ns
evening	0.15 ns	0.02 ns	-0.12 ns

None of the above calculations proved to be significant

C statistic results

Table 4-18-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	1.10 ns	1.29 ns
cont...ss	-0.58 ns	-1.14 ns
calmness	0.90 ns	0.50 ns
evening		
alertness	1.00 ns	0.65 ns
cont...ss	0.97 ns	0.80 ns
calmness	0.78 ns	-0.50 ns

None of the above calculations proved to be significant

(c) Hours of sleep

Table 4-18-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=13)			tryptophan(n=12)			placebo(n=6)
r1	r2	r3	r1	r2	r3	r1
-.48	.45*	-.29	-.18	-.27	-.18	.04

* exceeds the critical value for the .05 level of significance

t test results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
~ 1.08 ns	0.68 ns	-0.32 ns

Comment on hours of sleep

No significant changes emerged for hours of sleep in terms of the mean difference between baseline, tryptophan and placebo phases.

(d) Side effects

Table 4-18-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=14)			placebo(n=7)
r1	r2	r3	r1	r2	r3	r1
.49	.29	.21	-.18	-.11	-.12	.27

* exceeds the critical value for the .05 level of significance

t test results for side effect severity

base1 - tryp	base1 - plac	tryp - plac
~ 2.58 *	~-0.61 ns	~-1.39 ns

Comment on side effects

As is evident from the above results, a significantly higher level of side effects was apparent during the baseline period relative to the tryptophan phase.

4.2.18.5 Summary and Conclusions

As is evident from the consistently high SDS scores, a state of depression was maintained throughout the trial period with no evidence of reduced scores associated with tryptophan intake. There was no evidence from visual or statistical analysis of mood scale data to support therapeutic effects associated with tryptophan ingestion. Tryptophan intake was not associated with changes in total sleep time or increased side effect severity.

4.2.19 Subject 19

(1) Demographic variables

age(yrs): 43 sex: female height(cms):152
weight(kgs):52.00
(within desirable weight range)
tryptophan experience: - not consumed prior to this project
motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial and subsequent SDS scores for the present subject were all below the mean according to Knight et al.'s (1983) norms. On this basis and a general interest motivation for participation, this subject was not classed as depressed.

(b) Anxiety status

The Trait anxiety score (37) for the present subject was close to the mean according to Knight et al.'s (1983) norms and all State scores were below the respective mean. Consequently, this subject was considered to be free from significant levels of anxiety symptoms.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo
14days	14days	7days	7days

(c) Extra details

Scale completion time was regular with missing data limited to three mood scale ratings.

(4) Results and analysis

(a) Weekly scores

Table 4-19-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
scale							
zung	26	25	27	27	28	27	28
state	25	23	25	29	26	29	29
HSCL	76	64	70	74	68	65	63

Table 4-19-2 HSCL factor scores

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
factor							
1	1.08	1.00	1.00	1.07	1.07	1.00	1.07
2	1.34	1.34	1.36	1.34	1.34	1.34	1.24
3	1.72	1.13	1.46	1.47	1.29	1.25	1.12
4	1.26	1.09	1.37	1.45	1.09	1.09	1.09
5	1.15	1.00	1.15	1.15	1.15	1.15	1.00

Comment on weekly scale scores

Examination of the weekly scale scores (Tables 4-19-1 and 4-19-2) indicates the stabilty of low ratings across the entire trial with no noticeable changes between phases. HSCL factor scores were close to the means for a normal sample (Table 3-4).

(b) Mood factors

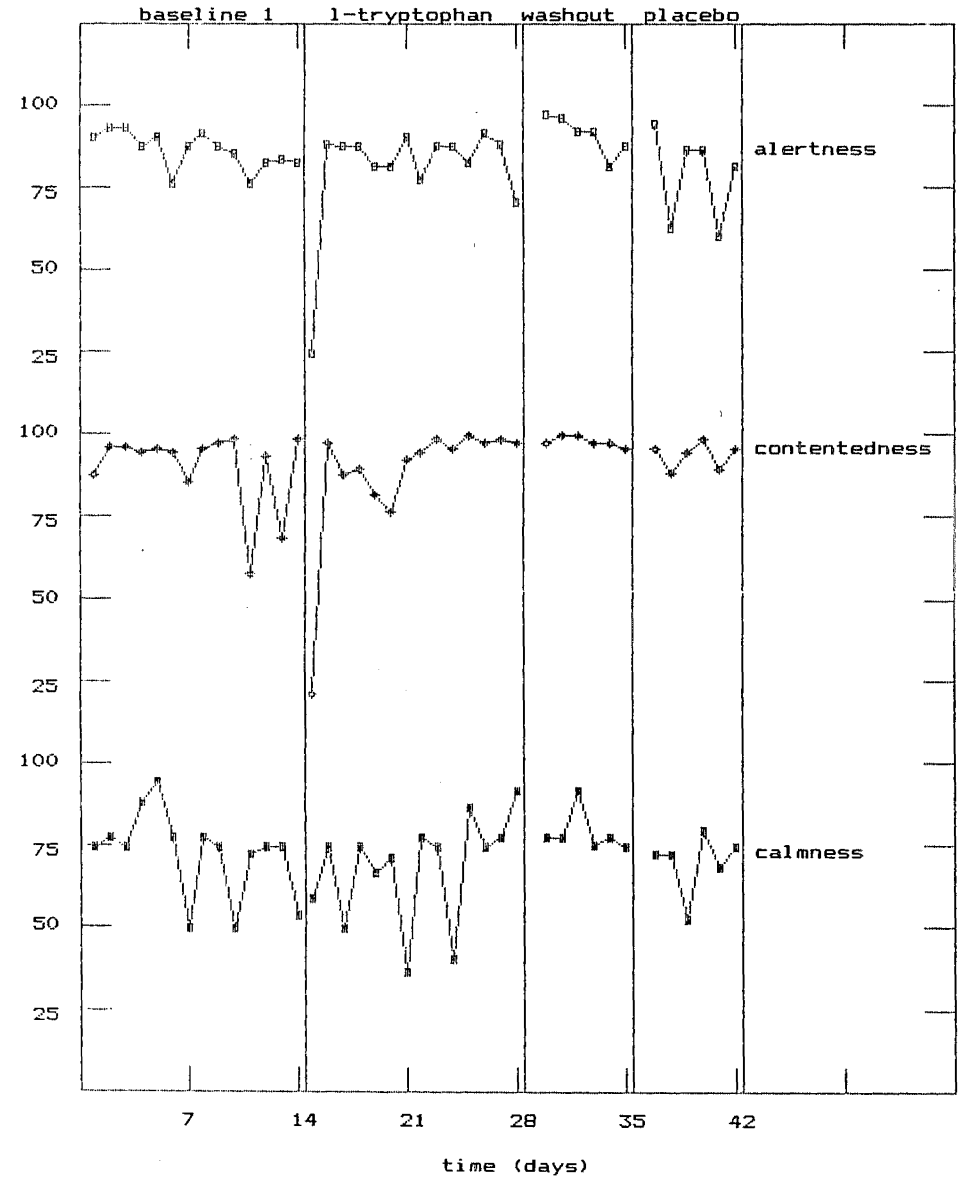
Visual analysis of graphed data

Graphs of morning and evening series for this subject appear in Figure 4-19. There was a slight increase in the level of evening alertness during the tryptophan phase relative to baseline. There was an extreme decline on morning alertness and contentedness dimensions for the first tryptophan rating which

Figure 4-19

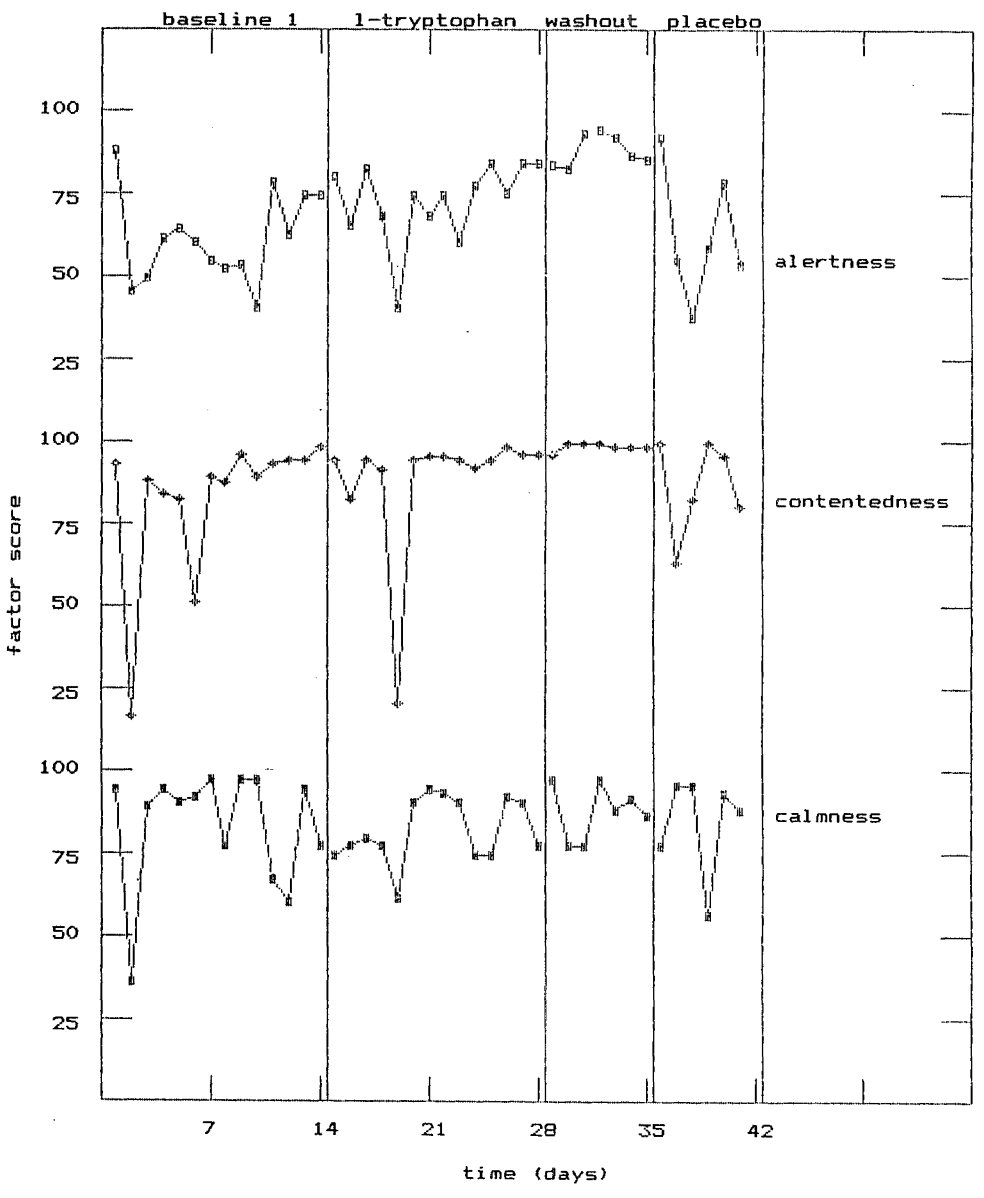
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 19



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 19



coincided with a dramatic elevation in reported side effects. The dips on all dimensions for the first baseline rating of the evening series did not relate to reports of unusual events or negative side effects. The evening dips on all dimensions (particularly contentedness) on day 5 of the tryptophan phase coincided with reports of tiredness and headaches.

Autocorrelation estimates

Table 4-19-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=14)			placebo(n=6)
	r1	r2	r3	r1	r2	r3	r1
alertness							
morning	.30	.11	-.10	-.07	-.07	-.03	-.53
evening	-.04	-.02	-.05	.04	.02	.17	-.08
cont...ss							
morning	-.25	.31	-.28	-.01	.08	.02	-.50
evening	-.09	.06	-.01	-.05	-.10	.05	-.19
calmness							
morning	.10	-.23	.17	-.27	.05	.27	-.52
evening	-.15	-.18	.07	.22	-.27	-.19	-.41

None of the above calculations proved significant

Table 4-19-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	~ 1.22 ns	~ 1.81 ns	0.23 ns
evening	-2.37 *	-0.13 ns	1.48 ns
contentedness			
morning	~ 0.36 ns	~-0.71 ns	~-1.06 ns
evening	-0.72 ns	-0.39 ns	0.21 ns
calmness			
morning	0.75 ns	0.40 ns	-0.26 ns
evening	~ 0.25 ns	-0.13 ns	-0.43 ns

* exceeds critical value for the .05 level of significance

- indicates the first mean of the pair is the lowest

~ phase differences unequal,t-test approximation used(see Chapter III)

Comment on t test results

As is evident from Table 4-19-4, the only statistically significant finding was for increased evening alertness during the tryptophan phase relative to baseline. However, this elevation was not maintained relative to the placebo condition.

C statistic results

Table 4-19-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	1.38 ns	0.04 ns
cont...ss	-0.92 ns	-0.88 ns
calmness	0.71 ns	-0.11 ns
evening		
alertness	1.38 ns	2.42 **
cont...ss	-0.25 ns	-0.18 ns
calmness	-0.52 ns	-0.20

** exceeds the critical value for the .01 level of significance

Comment on C statistic results

As indicated in Table 4-19-5, a significant departure in trend was indicated for the evening tryptophan phase on alertness relative to baseline.

(c) Hours of sleep

Table 4-19-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=14)			placebo(n=6)
r1	r2	r3	r1	r2	r3	r1
-.06	-.02	.03	-.30	.28	-.29	-.23

None of the above estimates proved significant

t test results for hours of sleep

base1 - tryp	base1 - plac	tryp - plac
~-0.15 ns	~-0.40 ns	~-1.17 ns

Comment on hours of sleep

No significant changes emerged for hours of sleep in terms of the mean difference between baseline, tryptophan and placebo phases.

(d) Side effects

Table 4-19-7 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=14)			placebo(n=6)
r1	r2	r3	r1	r2	r3	r1
-.01	-.01	-.02	.14	-.12	.24	.27

None of the above estimates proved significant

t test value results for side effect severity

base1 - tryp	base1 - plac	tryp - plac
-2.07 *	-2.51 *	0.18 ns

Comment on side effects

As indicated from the above t test results, side effect severity was higher during both tryptophan and placebo periods relative to baseline. The placebo period only consisted of six days. On this basis, comparison of the first six days of the tryptophan period with the placebo phase would have indicated a significantly higher level of symptoms for the tryptophan phase relative to placebo. That is, the increase in symptom severity associated with the tryptophan phase was essentially confined to the first five days with greatest severity noted on the first day. The most obvious symptom volunteered by the present subject concerned 10 reports of tiredness during the tryptophan phase. Only two other reports of tiredness were noted outside the tryptophan phase, i.e. within the placebo period.

(5) Summary and Conclusions

As is apparent from the foregoing analysis, low scores on all the weekly scales were maintained throughout the trial period, confirming the non-depressed and non-anxious status of this subject. The visual indication of increased alertness during the tryptophan phase relative to baseline in the evening was confirmed by statistical anaylsis on the basis of both t test and C statistic calculations. However, neither visual nor statistical analysis confirmed the tryptophan elevation to be significant relative to placebo ingestion.

The main finding for the present subject was the coincidence between the dramatic declines on the moodscales during the tryptophan period (i.e. on day 1 of the morning phase and day 5 for the evening phase - particularly for the alertness and contentedness dimensions) and reports of negative effects such as headaches and tiredness. Such findings were confined to the first five days of tryptophan intake. The level of side effects was found to be higher during both the tryptophan and placebo phases relative to baseline. However, the most severe levels were clearly confined to the first week of tryptophan intake. Thus tryptophan ingestion in the present subject, at 3gms/day for 14 days, could be most confidently associated with an increase in side effect severity for the first five days relative to baseline or placebo phases. There was a lack of evidence for consistent mood altering effects in relation to tryptophan intake, with declines on contentedness and alertness being confined to one or two days at the beginning of this phase.

4.2.20 Subject 20

(1) Demographic variables

age(yrs): 19 sex: male height(cms):173

weight(kgs):76.50

(within desirable weight range)

tryptophan experience: - not consumed prior to this project

motivation for participation: - general interest

(2) Psychological variables

(a) Depression status

The initial and subsequent SDS total scores for the present subject were all below the appropriate mean according to Knight et al.'s (1983) norms. On this basis and that of a general interest motivation for participation, this subject was not classed as depressed.

(b) Anxiety status

The Trait score (28) and all State anxiety scores were below the appropriate means according to Knight et al.'s (1983) norms. Thus, the present subject was considered to be free from elevated levels of anxiety.

(3) Experimental variables

(a) Dose level(gms/day): 3

(b) Phase description

baseline 1	tryptophan	washout	placebo
14days	14days	7days	7days

(c) Extra details

Scale completion time was regular with a relatively high level of missing data for daily mood ratings. The weekly ratings for the end of the second baseline week and the end of the first tryptophan week were also missed. No tablets were forgotten.

(4) Results and analysis

(a) Weekly scores

Table 4-20-1 Total scores for Zung, State anxiety and HSCL scales

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
scale							
zung	33	32	-	-	34	23	24
state	25	26	-	-	25	22	21
HSCL	66	62	-	65	67	59	61

Table 4-20-2 HSCL factor scores

	baseline 1			tryptophan		wash	placebo
day	01	07	14	21	28	35	42
factor							
1	1.46	1.12	-	1.40	1.29	1.09	1.23
2	1.00	1.12	-	1.00	1.00	1.00	1.00
3	1.00	1.00	-	1.18	1.33	1.00	1.00
4	1.10	1.00	-	1.00	1.00	1.00	1.00
5	1.00	1.00	-	1.00	1.00	1.00	1.00

Comment on weekly scale scores

No obvious between phase differences were apparent for total scores on the weekly scales. Low scores were maintained throughout the trial period. There was a slight elevation for factor 3 (interpersonal sensitivity) on the HSCL scale during the tryptophan phase which could not be meaningfully related to tryptophan intake. HSCL factor scores were close to the means for a normal sample (Table 3-4).

(b) Mood factors

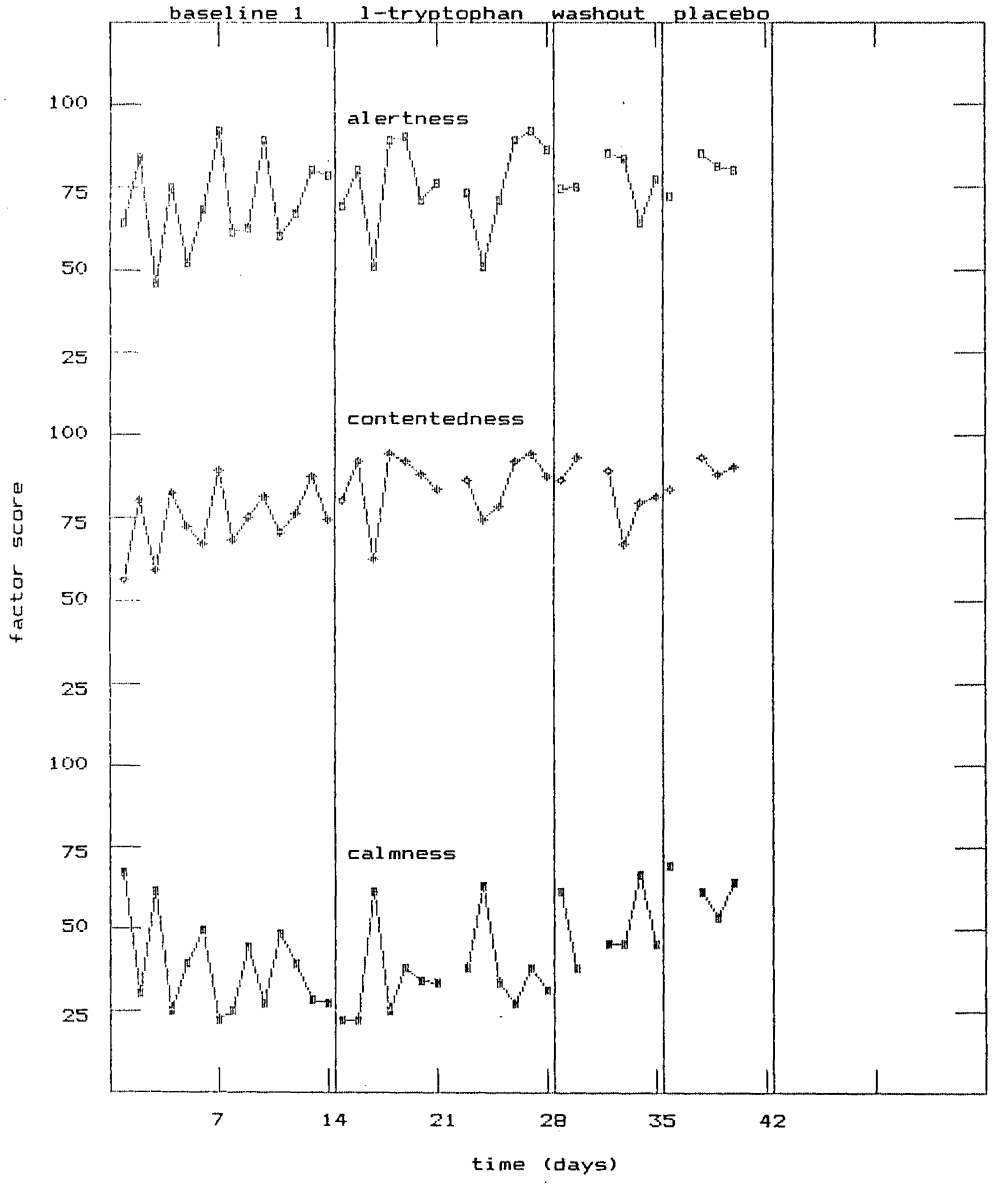
Visual analysis of graphed data

No consistent trends or changes could be detected on morning or evening series for this subject (Figure 4-20). Similarly, no

Figure 4-20

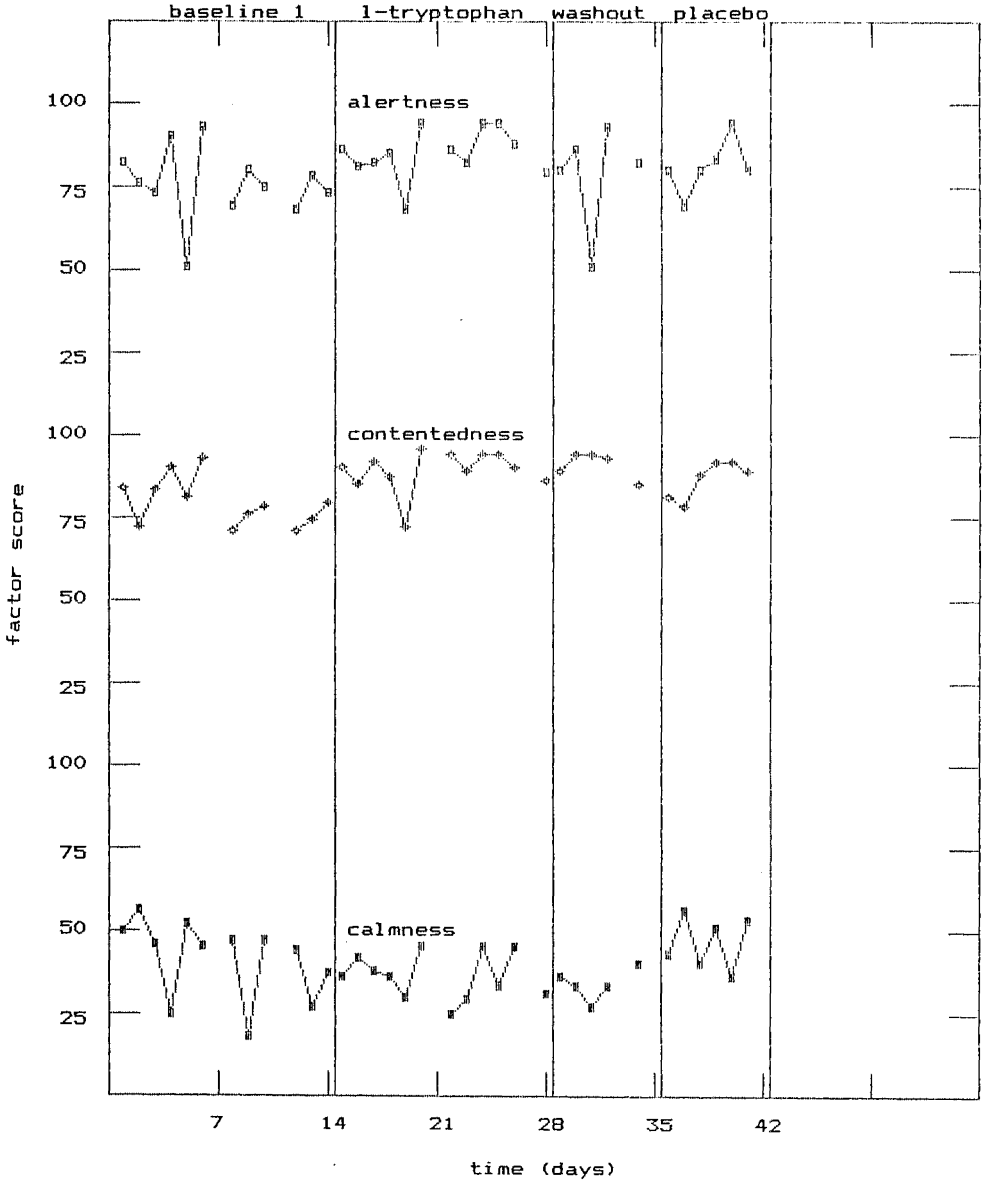
FACTOR SCORES FOR THREE MOOD DIMENSIONS - MORNING DATA

SUBJECT: 20



FACTOR SCORES FOR THREE MOOD DIMENSIONS - EVENING DATA

SUBJECT: 20



relationships between unusual events and changes in mood ratings were apparent. Occasional reports of alcohol consumption did not show any relationship to visually significant changes in the mood dimensions. However, alcohol consumption generally occurred after completion of the evening scales so that the closest ratings to this event were those for the morning after.

Autocorrelation estimates

Table 4-20-3 rk (k=1,n/4) values for separate morn. & eve. series

factor	baseline 1(n=14)			tryptophan(n=13)			placebo(n=6)
	r1	r2	r3	r1	r2	r3	r1
alertness							
morning	-.42	-.08	.29	.07	-.19	-.14	-
evening	-.76**	.41*	-.09	-.12	-.07	.19	.11
cont...ss							
morning	-.44	.20	.25	-.22	-.08	-.19	-
evening	-.01	.14	.11	-.10	-.27	.27	.50**
calmness							
morning	-.32	.18	.07	-.24	-.21	.06	-
evening	-.14	-.23	.02	-.44	.02	.06	-.76*

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results

Comment on t test results

As is indicated in Table 4-20-4, the alertness and contentedness dimensions were found to be significantly elevated in the evening during tryptophan and placebo phases relative to baseline. Morning contentedness during the tryptophan phase was significantly elevated relative to baseline. Finally, the level of calmness in the evening on the tryptophan phase was found to be significantly below placebo, but not baseline. Comparisons of placebo periods with baseline and tryptophan had to be omitted for all dimensions in the morning series owing to the high level of missing data during this period. In the case of the evening baseline-tryptophan difference, significance levels may have been

biased due to the presence of autocorrelation in the baseline phase. Similarly the placebo-baseline difference for evening contentedness and the placebo-tryptophan difference for evening calmness could not be interpreted confidently due to the presence of signifcant negative autocorrelation.

Table 4-20-4 t test values for mean differences between baseline 1, tryptophan and placebo phases

	base1 - tryp	base1 - plac	tryp - plac
alertness			
morning	-1.17 ns		
evening	-2.43 *+	-2.30 *	-0.50 ns
contentedness			
morning	-2.94 **		
evening	-3.50 **	-2.15 *+	0.77 ns
calmness			
morning	0.41 ns		
evening	~ 1.24 ns	-0.99 ns	-2.83 *+

* exceeds critical value for the .05 level of significance

** exceeds critical value for the .01 level of significance

\+ sig. t values affected by sig. levels of autocorrelation

\- indicates the first mean of the pair is the lowest

C statistic results

Table 4-20-5 Z values for morning, evening and combined series

series	base1	bs1+tryp
morning		
alertness	-1.62 ns	-0.57 ns
cont...ss	-1.21 ns	0.33 ns
calmness	-0.53 ns	-0.81 ns
evening		
alertness	-2.80 **	~-2.07 *
cont...ss	0.03 ns	1.52 ns
calmness	-0.43 ns	-0.56 ns

** exceeds the critical value for the .01 level of significance

~ due to a sig. trend in the base1 phase, this calculation was based on a comparison series (see Chapter III for explanation)

Comment on C statistic results

As indicated in Table 4-20-5, the tryptophan period demonstrated a significant departure in trend from baseline in the evening series only.

(c) Hours of sleep

Table 4-20-6 Autocorrelation estimates: rk (k=n/4) values

baseline1(n=14)			tryptophan(n=13)		
r1	r2	r3	r1	r2	r3
.41*	-.20	-.62**	-.18	-.50*	.39*

* exceeds the critical value for the .05 level of significance

** exceeds the critical value for the .01 level of significance

t test results for hours of sleep

base1 - tryp

-0.73 ns

Comment on hours of sleep

As evident from the t test result, no significant difference could be established between the baseline and tryptophan periods for hours of sleep.

(d) Side effects

No side effects were reported by the present subject throughout the trial period.

(5) Summary and Conclusions

As indicated in the foregoing description this subject was not considered to be depressed or particularly anxious on the basis of depression and anxiety scores relative to Knight et al.'s (1983) norms.

The relatively high level of missing data in conjunction with the brief placebo period limited the validity of visual and statistical analysis for this subject. Given these limitations, statistically significant findings for changes in level between phases were limted to a placebo elevation on alertness relative to baseline in the evening and a tryptophan elevation on contentedness relative to baseline, in the morning and evening. However, confident visual support could not be given to such statistical outcomes. The significant C statistic result, demonstrating a departure in trend for the tryptophan phase relative to baseline in the evening, was also unsupported by visual analysis.

No significant difference was detected between baseline and tryptophan periods for hours of sleep and there were no reports of negative side effects for the total trial period. Thus, no changes for general mood, side effect experience or total sleep time could confidently be associated with ingestion of 3gms/day of tryptophan over a 14 day period in the present subject.

4.3 SAMPLE PROFILE AND EVALUATION

4.3.1 Sample descritpion

(a) Sex

males (N=10) females (N=10)

(b) Age (years)

mean = 31 min = 19 max = 60

distribution

category	N
19-24	8
25-30	2
31-36	3
37-42	4
43-48	2
49-54	-
55-60	1

(c) weight-height relationships

Although no attempt was made to relate dose level with weight to height ratio or to body weight in the present study it seems probable that significant relationships may emerge between dose to weight ratios, tryptophan response and/or side effects. There is also evidence to support differences in brain serotonin metabolism in relation to weight level (Kaye et al., 1984). Recommended dose levels were obtained from Bray (1978). These levels were recognized by the 'Royal College of Physicians of London' in 1983.

weight-height category	N
below recommended range	2
within recommended range	15
above recommended range	3

(d) Marital status

category	N
single	11
defacto	2
married	5
divorced	1
separated	
widowed	1

(e) Living situation

category	N
alone	2
sharing (excl. spouse)	10
with spouse	6
with parents	2
with children	4
other	-

(f) Highest education level

category	N
primary	-
4th form	-
school cert.	-
U.E.	5
tech. qualif.	1
univ. degree	14
other	-

(g) Occupations

category	N
student	13
paid empl.	9
unempl (reg.)	4
homemaker	4
retired	1

(h) Medical or psychological conditions

As noted previously, subjects were excluded if they experienced any of the medical/psychological conditions described on the demographic questionnaire.

(i) Drug consumption

At entry to the program two subjects were regularly consuming prescribed doses of antidepressants and one of these subjects was concurrently consuming tranquilizers. Subject 02 continued with his prescribed therapeutic medication of 50mg clomipramine/day and 2mg lorazepam/day throughout the trial. Subject 16: was taking 60mg mianserin/day and ceased intake two weeks prior to the commencement of tryptophan ingestion. Finally there were six regular consumers i.e. daily of different vitamin supplements. Four subjects admitted occasional consumption of analgesics, five to occasional consumption of marijuana and one to occasional consumption of diet medication.

(j) Information relevant to female participants

No subjects admitted to being pregnant on entry to the program and three were regulary taking chemical contraceptives. Six of the ten females reported suffering from premenstrual tension.

(k) Tryptophan experience

Two of the 20 participants had previously consumed tryptophan. Subject 01 had taken it occasionally as a diet supplement. Subject 16 had taken it on a short term basis and low dose (3gms/day) for stress relief . In neither case could subjects recall any noticeable effects.

(l) Vegetarian

Seven of the 20 participants said they were vegetarian.

(m) Motivation for participation

The motivations for participation, as stated by subjects on entry to the program, can be classified into three general categories:

category	N
general interest	11
depression	8
anxiety	1

The two most depressed subjects also gave anxiety or stress as a reason for participation. This was corroborated by both subjects exhibiting high Trait anxiety scores.

(n) Zung depression scale scores

mean = 36.30 min = 24.00 max = 53.00

Depression status (based on Zung's (1972) categories)

	N
normal (not depressed)	13
mild-moderate depression	5
moderate to severe	2

The above categorization was based on ratings at the point of entry to the program. The five individuals classed as depressed on Zung's (1972) scheme also gave their motivation for participation as depression. In addition, three individuals classified as non-depressed under this scheme also gave their reason for participating as depression. One of these three was currently taking prescribed antidepressants on entry to the study and the other two had been taking antidepressant medication in the recent past. On this basis 8 out of the 20 participants were classified as depressed.

(o) STAI scores

Trait

mean = 42.10 min = 26 max = 70

With reference to the appropriate norms for age and sex (Knight et al., 1983), the present sample can be classified as follows:

category	N
< 1 SD above the mean	12
1-2 SDs above the mean	4
2-3 SDs above the mean	1
> 3 SDs above the mean	3

If subjects' scores are considered with respect to Spielberger's (1970) norms based on depressed and anxious male psychiatric patients (see Table 3-3), then certain individuals scores could be considered more in keeping with this classification. That is, the eight subjects with scores exceeded

one SD above Knight et al.'s (1983) means exhibit scores close to Spielberger's (1970) norms.

A fairly systematic relationship between (1) depression as the motivation for participation, (2)elevated SDS scores, and (3)elevated Trait anxiety scores is apparent for the present sample. The relationship of the last two variables is substatiated by the more general finding of a high correlation (.90) between SDS and Trait anxiety scores for the whole sample on entry to the program. Knight et al. (1983) have also reported a relatively high correlation of .70 for the above scales in their (n=1173) normal sample.

State

mean = 36.90 min = 25 max = 67

Once again, with reference to Knight et al.'s (1983) norms the sample can be classified as follows:

category	N
< 1 SD above the mean	13
1-2 SDs above the mean	4
2-3 SDs above the mean	1
3-4 SDs above the mean	1
> 4 SDs above the mean	1

Six of the eight subjects with Trait scores exceeding one SD above the mean also exhibited State scores in this range. However, the overall relationship between State and Trait scores does not appear as consistent as that for Trait and Zung scores. That is, a correlation of only .69 was achieved between Trait and State scores for the sample as a whole. This is again in keeping with findings by Knight et al. (1983) who reported a .65 correlation between these scales.

4.3.2 Overview of the sample

The sample could be considered to consist of predominantly young, single university students - equally represented by both sexes. Most subjects conformed to desirable weight to height

ratios and were apparently free from chronic medical or psychological conditions. Seven out of twenty participants were stated vegetarians.

Two distinct psychological groups were considered in the evaluation. The first group consisted of 'non-depressed' subjects. Eleven of this group gave a motivation for participation of 'general interest' and exhibited no notable elevations on SDS or STAI scores (in relation to Knight et al.'s (1983) norms) at entry to the program. The remaining subject in this group reported experience of slight levels of anxiety prior to entry to the program, and this was supported by moderately elevated STAI scores.

The second group included five subjects classified as depressed on the basis of Zung's (1972) classification who also gave 'depression' as their motivation for participation and exhibited elevated Trait anxiety scores. The remaining three subjects in this group expressed the same motivation for participation and were either consuming antidepressants at entry to the trial or had been in the recent past.

4.3.3 Evaluation of tryptophan administration for the sample

This section provides a broad overview of the experimental outcome for the sample as a whole.

4.3.3.1 General mood altering effects

If attention is limited to findings supported by both statistical and visual analysis and to differences for tryptophan relative to both placebo and baseline phases, then for 18 of the 20 participants no significant relationships could be established between tryptophan ingestion and mood alteration. Results for the remaining two subjects were only indicative of slight associations. In the first case (subject 11), the finding was a reduced evening alertness level associated with tryptophan intake and in the second case (subject 17) an increase in morning contentedness associated with tryptophan intake.

If consideration is extended to cases where the placebo phase was absent or inadequate (too brief or missing large amounts of data) then a few further associations are apparent for tryptophan administration relative to baseline. For subjects 10 and 15 a significant reduction in morning alertness was apparent for the tryptophan phase and this effect was maintained into the evening for subject 15. Once again the reduction was slight in both cases but in keeping with past reports of tryptophan's psychological effects. Both subjects 10 and 15 were classified as non-depressed. For subject 8, visual and statistical analysis supported a significant but slight increase in evening calmness relative to baseline.

Finally, when consideration was extended to effects associated with tryptophan intake, which were significant relative to baseline but not to placebo, the number of significant associations between tryptophan intake and mood alteration increased. For subject 12, a slight increase in morning and evening contentedness was apparent for tryptophan relative to baseline, while an evening reduction in tryptophan contentedness relative to baseline was apparent for subject 05. In addition, a reduction in morning alertness was associated with tryptophan intake in subject 14 and an increase in evening alertness in subject 19.

As is apparent from the above discussion, the number of significant relationships between tryptophan intake and mood alteration increases as the criteria for change are reduced from significant tryptophan-placebo differences to significant tryptophan-baseline differences. The most general finding was for reduced alertness for one or both series in 4 subjects. These subjects could not be distinguished from the rest of the sample with respect to any relevant psychological or experimental variables. The only other finding to extend beyond one subject was for an increase in contentedness associated with tryptophan intake. This slight elevation was indicated for two individuals both of whom were classified as depressed.

The psychological significance of the above findings is uncertain in view of the slight differences involved. In no case

did subjects indicate noticeable awareness of the states by additional daily comments or following retrospective assessment at the trial termination. The main finding across subjects of reduced alertness, while limited to 4 subjects and of slight magnitude in all cases, could be considered in keeping with evidence from past studies of increased drowsiness in relation to tryptophan intake (Yuwiler et al., 1981; Carroll et al, 1970; Smith & Prockop, 1962; Charney et al., 1982; Shopsin, 1978).

4.3.3.2 Therapeutic effects

Consideration of antidepressant effects was limited to eight subjects i.e. subjects 02,03,09,11,12 who were classified as experiencing/exhibiting mild to moderate levels of depression, subjects 16 and 18 classified as suffering moderate to severe depression and subject 17 whose depressed status could not be confirmed with respect to SDS scores. In addition, attention was given to evidence for anxiolytic effects in six of the above subjects and two additional participants demonstrating elevated anxiety levels. That is, subject 10 was considered to be experiencing slight anxiety and volunteered this as a tendency on entering the trial. Subjects 02 and 15 were classified as exhibiting moderate levels of anxiety and subjects 03,09,11,12 and 16 as demonstrating high levels of anxiety relative to Knight et al.'s (1983) norms.

Slight reductions were apparent for the tryptophan period relative to baseline on Zung and State scores as well as the depression and anxiety dimensions of the HSCL for subject 12. Similarly for subject 18, there was a noticable decline on the Zung score after the second week of tryptophan ingestion. However, in neither case were the changes significant relative to placebo periods. Reductions in weekly scale scores were not apparent for other subjects.

For 6 of the 10 subjects considered in this section, i.e. 02,03,10,11,15 and 18 there was insufficient statistical or visual evidence to support elevation on any of the mood dimensions. In addition, for subject 16 there was no evidence to support changes during the tryptophan period relative to

mianserin. For subject 09, a statistically significant elevation in the level of contentedness was apparent in the evening relative to baseline and placebo. However, the importance of this finding could not be confirmed by visual analysis. Statistical and visual analysis confirmed a slight increase for subject 12 in morning and evening contentedness relative to baseline but not placebo. For subject 17 a slight elevation in morning contentedness was indicated following visual and statistical analysis and this effect was significant relative to both baseline and placebo phases.

Thus, slight reductions in weekly depression and anxiety dimensions were indicated for subject 12 and slight increases in contentedness for subjects 12 and 17. However, in neither case were such changes interpreted as representing significant therapeutic effects. For subject 12, SDS scores showed only slight reductions and did not drop below Zung's (1972) 'mild to moderate' depression category except on one occasion during the tryptophan phase. Similarly, State anxiety scores still remained significantly elevated relative to Knight et al.'s (1983) norms. Even if such changes could be considered to represent true therapeutic effects, then they were not in excess of placebo change and were only slight relative to baseline levels. Subject 12 was also unaware of any improvement in affective state associated with tryptophan intake following questioning at the end of the trial. While subject 17 gave a motivation for participation of depression and claimed to have much improved while taking tryptophan, total SDS scores gave no confirmation of this status or of a reduction in association with tryptophan intake. While it is possible that the increase in morning contentedness was reflective of a psychologically significant response to tryptophan ingestion, the elevation was not maintained into the evening.

4.3.3.3 Effects on total sleep time

There was no significant difference in mean hours of sleep between tryptophan and baseline or placebo periods for 18 subjects. In the remaining two cases change for the tryptophan phase was significant relative to baseline but not placebo

periods. For subject 2, the mean hours of sleep during the tryptophan phase was significantly below baseline, while for subject 15 the mean was significantly above baseline. In both cases the obtained differences were statistically small. For two subjects (10 and 16) comparisons with the tryptophan phase were not possible due to missing ratings or phases. For subject 16, application of the C statistic to the tryptophan phase indicated no trends in total sleep time over the 21 day period.

There is some uncertainty as to the consistency within and across subjects for total sleep estimation. That is, it is not clear whether estimates were tied to the time of retiring or the conjectured time of sleep onset. Whatever the case, there was no emergence of general effects across subjects for total hours of sleep in relation to tryptophan intake.

4.3.3.4 Side effects

As is evident from the conclusions for individual subjects, associations between negative side effects and tryptophan intake were frequent and often represented the most dramatic and consistent of all relationships.

No quantitative or qualitative effects were apparent for 11 out of 20 subjects. For three subjects (02, 11 and 12) clear increases in side effect severity during the tryptophan phases were evident relative to baseline and placebo periods. In addition, significant marked elevations in severity were apparent for subjects 03 and 19, relative to baseline only. For subject 19 the placebo phase only consisted of 6 days. If this phase had been compared with the first six days of the tryptophan period, then severity for the tryptophan phase would have been significantly elevated relative to placebo. That is, most of the increase in side effects during the tryptophan phase (for subject 19) was confined to the first 5 days.

In all the above cases of elevation in tryptophan side effect severity, the placebo phase also showed significant elevation relative to baseline. Dramatic elevations in side effects following placebo administration have been reported

previously (Green, 1964). Four of the above five subjects, exhibiting tryptophan elevations in side effect severity, were classified as depressed. As in the case of significant mood changes associated with placebo intake, elevation in side effects may have been contributed to by phase order. That is, experience of side effects during tryptophan intake may have carried over in the form of expectancies to the placebo phase. In this case, one would expect qualitative similarities between tryptophan and placebo periods. In fact Green (1964) noted that placebo side effects in experiments where placebo served as the control for the active drug were almost invariably similar to those experienced with the active drug itself. While this was true to some extent in the present study there were also large increases in symptoms unique to the tryptophan phase. Also, some similarity between tryptophan and placebo symptoms seems inevitable due to the selective focus on a few symptoms considered relevant to tryptophan intake.

Nine subjects exhibited noticeable elevations in symptoms that were unique to the tryptophan phase, the most common symptom being 'increased appetite' for four subjects. Other reports were of increased constipation in two subjects, and abdominal cramps during the first week for another two individuals. Subject one experienced virtually no symptoms until day 14 of the tryptophan phase, when she reported dramatic effects in keeping with the 'niacin reaction' (described in Chapter II). The niacin reaction may also be relevant to subject 02 where reports of hot flushes were frequent during the tryptophan phase but not during other periods. Finally, further dramatic increases for single subjects during the tryptophan phase were associated with symptoms such as headaches, extreme tiredness and dry mouth.

Four of the five subjects experiencing notable increases in symptom severity were classified as depressed. Experience of side effects could not be consistently related to dose level. While four of the subjects experiencing significant side effect increases were on the maximun dose of 6gms/day, a further three subjects on this dose and two on the next highest level of 4gms/day experienced no noticeable increases.

4.4 EXPERIMENTAL DISCUSSION

This section is concerned with a discussion of factors relevant to the present experiment which may act to limit the validity and generality of the foregoing results.

4.4.1 Psychological status of the participants

On the basis that 12 of the 20 participants were not depressed it could be speculated that most subjects were primed more towards the expectation of negative side effects rather than positive therapeutic benefits. Some empirical support for such a speculation comes from a study by Green (1964) where the incidence of reported side effects was significantly greater following placebo for well subjects than for psychiatric (including depressed) patients.

The classification of depressed subjects in the present study remains somewhat dubious. That is, at most, the criteria for a classification of 'depression' depended on a motivation of such for participation, demonstration of SDS total scores within Zung's (1972) 'moderate - severe' category and finally, information relating to recent consumption of prescribed antidepressant or hypnotic medication. Similarly, judgements that subjects exhibited relatively high levels of anxiety were simply based on Trait and State scores considered to be exceptionally elevated relative to Knight et al.'s (1983) norms and information relating to recent consumption of anxiolytic medication. Such criteria clearly fall short of those required for a formal diagnosis of depression or anxiety based on systems such as the DSM III and are essentially limited to estimates of the severity of depression with no qualitative evaluation. Thus, results may not be generalizable to depressed and anxious individuals classified by alternative criteria.

4.4.2 Other subject variables

(a) Age

As indicated in the sample description, the majority of participants were young, i.e. within the 19-24 age group. While there were no clear relationships between age and outcome in the present study, there is evidence of plasma tryptophan concentration being age related (Banki & Molnar, 1981 (a) & (b)). If it is assumed that this parameter bears relvance to central utilization of tryptophan loads then the present results should not be freely generalized to older age groups.

(b) Contraception and premenstrual tension

Two of the three subects consuming chemical contraceptives were classified as depressed. Neither of these subjects exhibited significant antidepressant responses. It has been claimed that depressive syndromes induced by oral contraceptives relate to a disruption of tryptophan metabolism which reduces brain serotonin concentration (Malek-Ahmadi & Behrmann, 1976; Leeton, 1974). It was not clear whether these subjects' depressions related to contraceptive intake. However, it could be speculated that the lack of therapeutic response in these cases related to contraceptive induced disorders of tryptophan metabolism.

No clear relationships were apparent between sex and psychological status of subjects or general mood altering effects. Three of the female subjects expressing significant elevations in side effects during tryptophan ingestion also admitted to suffering from premenstrual tension. In each case there was some overlap between the tryptophan period and a two week premenstrual phase. Where it was possible to compare the premenstrual phase coinciding with tryptophan intake with another phase, it was evident that the premenstrual period could not account for the total rise in tryptophan related side effects. Still, it is possible that premenstrual symptoms confounded the tryptophan side effect elevation for these subjects.

(c) Weight to height relationships

Subject 01 was considered to be below the desirable range and subjects 07, 10 and 15 above this range (Bray, 1978). In the case of subject 01, the dramatic experience of a potential 'niacin reaction' during tryptophan intake may have been attributable to a low height to weight level in combination with a high 6gms/day dose. In the subjects above the desirable weight to height range it could be argued that the lack of general mood altering effects was attributable to inadequate dosage relative to body weight i.e. 2gms/day for one and 3gms/day for the other two. Certainly, these three subjects did not exhibit any noticable elevation in side effects in relation to tryptophan intake.

(d) Vegetarianism

The seven vegetarians could not be distinguished from the rest of the sample with respect to mood change, therapeutic efficacy or side effect expression. However, on the basis of tryptophan - diet relationships considered in Chapter III, dose level requirements may be expected to differ between omnivores and vegetarians.

4.4.3 Experimental variables

Experimental conditions exhibiting most variation between subjects were dose level and the phase length for tryptophan administration.

(a) Dose level

Dose level varied between 2 and 6gms/day across subjects. This variable could not be related to differences in general mood change, therapeutic effects or side effects.

While specific dose recommendations have been made regarding optimal therapeutic levels (Chouinard et al., 1978), such doses have not been related to body weight. Thus, the lack of therapeutic effect in depressed subjects receiving the

recommended 6gms/day (n=3) may have related to a dosage inappropriate to body weight. In the remaining five 'depressed' subjects receiving 3gms/day, such a dose would be regarded as inadequate, by Chouinard et al.'s (1978) standards, to effect a significant antidepressant response. However, significant antidepressant effects have been documented for doses of 3gms/day (Kline & Shah, 1974). While Walinder et al. (1976) demonstrated 150mg/day clomipramine + 3gms/day tryptophan to be significantly more effective than clomipramine alone, it is possible in the case of subject 02 that the concomitant intake of 50mg/day of clomipramine made consumption of 6gms/day tryptophan therapeutically excessive.

Since it was not possible in the present study to investigate tryptophan dose variation within subjects, it must be considered that inappropriate levels in some individuals may have contributed to a lack of mood altering or therapeutic effects or to an elevation of side effects. If optimal therapeutic doses are in fact confirmed to be in the order of 6gms/day, the declination by the majority of subjects in the present study to consume this quantity (i.e. 12x0.5 mg tablets) may indicate a practical drawback to the therapeutic or general research value of tryptophan.

(b) Tryptophan phase length

Five of the eight depressed subjects were considered to have completed trial lengths of sufficient duration for the detection of antidepressant effects (i.e: greater than 21 days). Although significant antidepressant effects have been detected as soon as seven days following therapeutic administration of tryptophan (Moller et al., 1980), it must be considered that tryptophan periods of 11 and 14 days for the remaining three subjects may have been inadequate. Therapeutic effects for other common antidepressant drugs (tricyclics and MAOI's) are unlikely to emerge for 2-4 weeks (Duquesne & Reeves, 1982).

The required trial period for a valid analysis of general mood altering effects in non depressed subjects is uncertain. Although some significant psychological effects have been

detected as soon as 2 hours after a single tryptophan load in normal subjects (Yuwiler et al., 1981; Greenwood et al., 1974; 1975; Smith & Prockop, 1962; Charney et al., 1982) such reactions have typically been in the class of negative side effects, e.g. drowsiness, lethargy and nausea. Only one non depressed subject completed a tryptophan phase of greater than 14 days, thus it must be considered that phase lengths for the remaining 11 participants may have been inadequate for the detection of general mood altering effects.

(c) Tryptophan administration procedures

The consumption of tryptophan as a single dose after completion of the evening mood scale (by all subjects), meant that the psychological ratings closest to tryptophan consumption occurred approximately 8 hours after ingestion. As stated in Chapter II, studies investigating the effects of acute tryptophan administration on plasma levels and psychological state indicated that free plasma concentrations were returning to baseline levels after about 6 hours. The same pattern was still apparent after 7-9 days administration (Yuwiler et al., 1981). While significant mood altering effects have been demonstrated following single daily dose schedules (Jensen et al., 1975; Lindberg et al., 1979) the majority of studies indicating positive mood altering effects, e.g. antidepressant properties have involved administration of two or three divided daily doses (Chouinard et al, 1979; Herrington et al., 1976; Rao & Broadhurst, 1976; Thomson et al., 1982).

Although, from a physiological veiw point it may have been more desirable to have employed an administration regime of two or three divided daily doses, there remain various practical and psychological reasons, discussed in Chapter III, for adhering to the single nightly schedule following evening mood ratings. Thus, it is possible that if psychological ratings had occurred closer in time to tryptophan ingestion or if tryptophan intake had been divided throughout the day, that the pattern of results would have been signifcantly altered.

(d) Sensitivity and appropriateness of psychological scales

The requirement for self rating scales which could both be applied to a heterogeneous psychological sample and bear relevance to the psychology of tryptophan administration may have compromized sensitivity of measurements for some subjects. As already mentioned, in the case of subject 17, the Zung total and the VAMS factor scores may have been insensitive or inappropriate to the kind of depression this subject claimed to have experienced and obtained relief from, following tryptophan consumption. Although there were no other dramatic discrepancies between empirical findings and subjective comments, it is still possible that certain scales may have been inadequate in the detection of effects relevant to the experimental inquiry for some participants.

While single VAMS dimensions have demonstrated significant sensitivity to tryptophan effects in normal subjects (Greenwood et al., 1974; 1975), it is possible that the condensation of dimensions to the three factor structures determined by Bond & Lader (1974) were inappropriate to detection of tryptophan effects in certain participants. As discussed in Chapter III, the alternative of determining factor structures relevant to depressed and non depressed groups in the present sample was not justifiable. Thus, Bond & Lader's (1974) factors of 'alertness' 'contendedness' and 'calmness' may have have been inappropriate to detection of tryptophan effects in the present sample. Also, while the above dimensions showed sensitivity in several subjects to effects expected to alter mood, e.g. flu and tiredness they may have been inadequate to detect more subtle psychological changes associated with tryptophan intake.

Given that past demonstrations of the VAMS sensitivity were limited to normal subjects, these scales may have been less relevant to depressed individuals in the present study. Examination of ratings on each dimension for depressed individuals did not, however, indicate limitation of ratings to the extreme ends of scales in any case. That is, as with the non depressed subjects, ratings for depressed individuals covered a reasonable range of the dimension and rarely hit the end points.

Although, SDS total scores have gained a reputation as reliable quantifiers of depressive states, this does not preclude the possibility that the index may have been inadequate to detect and monitor of the type of depression changes subject 17 claimed to experience. Also, the use of total scores for the Zung and STAI scales may have reduced the sensitivity of these scales in the present sample relative to item/factor scores.

Reliance on self rating procedures, in the present study, may have contributed to distortions peculiar to this mode of evaluation. For example, Hersen & Barlow (1976) cite evidence from the behavioural literature to suggest that self evaluation may be a reactive process, that is, by virtue of only monitoring and recording certain behaviours, the rates of such behaviours will change despite the absence of therapeutic intervention. In fact, some authors e.g. Johnson & White (1971), have proposed employing self monitoring as a deliberate manipulation for behaviour change. The specific effect of this kind of process on experimental outcome is uncertain. However, it is possible that 'other rater' procedures might have altered the experimental outcome.

Another confounding factor which may be exaggerated under self assessment conditions relates to the phenomena of 'demand characteristics'. That is, the tendency for response to be in favour of the experimental hypotheses when the subject is aware of their existence. Although subjects were not informed of the specific focus of the psychological states under study, familiarity with the scales may have oriented subjects attention towards relevant dimensions. While placebo periods might be expected to control for such influences it is also possible that subject awareness of the objects of inquiry may have contributed to placebo changes similar to those exhibited during tryptophan periods.

Another uncertainty with respect to self assessment procedures concerns the consistency of subjects in their ability to evaluate and rate psychological states as these processes change across time. Here the question arises as to whether the subject can perform the process of self assessment in as reliable

and meaningful a way while experiencing disturbed states, as at times of adaptive/normal functioning. As discussed in Chapter II, concern is frequently voiced over the reliability and validity of self assessment procedures in severely depressed individuals. However, on the basis of depression measures in the present study, most depressed subjects were only considered to exhibit moderate levels of depresssion.

(e) Other experimental variables

The potential bias resulting from the tryptophan - placebo phase order for 19 out of 20 subjects must be considered as a limitation to the generality of findings, given demonstrations that variables such as phase order may significantly and predictably alter experimental outcome (Wittenborn, 1978; Koch et al, 1983).

The absence of adequate placebo and baseline phases for comparison was a clear limitation to valid interpretation of outcome in certain individuals. However, most importance was attached to outcomes which could be supported by both statistical and visual analysis and were significant in relation to both baseline and placebo conditions.

Given the relative absence of therapeutic or general mood altering effects within subjects, factors such as spontaneous remission coinciding with changing conditions need not be considered in the present experiment. Other potential threats to longitudinal designs, such as waning enthusiasm and changing commitment to experimental tasks over time were not indicated in the present study. That is, no obvious effects such as lack of scale completion or failure to consume tablets were noted to increase with time. However, less easily detectable effects such as attention to accurate scale completion may have changed over the trial period.

It is conceivable that a seven day washout phase between tryptophan and placebo periods was pharmacologically inadequate for some individuals. Consequently, it is possible that carry over effects with a physiological basis in addition to those in

the form of expectancies (discussed in section 5.1) from tryptophan to placebo phases may have led to a conservative bias in the interpretation of phase differences.

As indicated in Chapter III, it was hoped that informing subjects that they could receive placebo or tryptophan on any night of both phases would reduce expectancies relating to phases differences. Exposure to both conditions within subjects is more likely to reinforce perceptions of differences between conditions than in group designs where each individual is typically exposed to only one treatment. However, no subject indicated awareness of receiving only one substance per phase at trial completion.

The interactive importance of the above variables as potential contributors to the the generality and validity of experimental outcome may well be greater than that indicated by each factor alone. However, given the known diversity between subjects in terms of psychological and experimental variables it was not considered justifiable to perform any multivariate statistical procedures on data across subjects. In addition, such a procedure would have been contrary to the theoretically more valid approach of focusing on experimental outcome within subjects.

CHAPTER V

SUMMARY AND CONCLUSIONS

5.1 EXPERIMENTAL

Outcome from the present investigation indicated a lack of dramatic or consistent relationships between tryptophan administration and psychological state within or across normal and depressed individuals.

The most consistent changes on VAMS dimensions, associated with tryptophan ingestion, were for reduced alertness in four subjects and increased contentedness in another two depressed individuals. However, only in two of the above cases were findings maintained relative to both baseline and placebo phases. Two of the findings were not significant relative to placebo, and the remaining two had missing or inadequate placebo phases for the purposes of valid comparison. Changes in all cases were statistically and visually slight and did not warrant comment by subjects at any point throughout the trial.

There was a lack of empirical evidence to indicate significant therapeutic effects (i.e. antidepressant or antianxiety) on the basis of Zung, State Anxiety, HSCL scores and the daily mood factors for most of the 10 subjects (8 depressed, 2 anxious) considered. Small reductions on weekly measures of depression and anxiety and increases in daily contentedness for one depressed subject (12) were significant only relative to baseline periods. Thus, if such trends were indicative of therapeutic change they were not maintained relative to placebo.

The most dramatic feature within and the most consistent pattern across subjects during tryptophan intake was limited to an increase in the severity and quality of side effects for nine subjects. There was reasonable variability in the type of symptom elevations between subjects, although increased appetite was

frequently and exclusively reported during the tryptophan period by four individuals. Tryptophan intake was not associated with any dramatic change in total hours of sleep for any subjects. While this parameter has shown significant effects in the past (Hartmann, 1976), it appears sleep latency is probably a more pertinent sleep index in relation to tryptophan intake. This point is further elaborated in the final part of this chapter.

It is possible that the requirement for statistical and visual criteria of change to be met before results were considered seriously, may have led to a conservative bias in the evaluation of outcome. However, the threat from type II errors is unlikely to be great, given the slight magnitude of effects demonstrated in all cases.

The generality and validity of the above outcome pattern was limited by the various design and methodological features discussed in Chapter IV. While comparison of experimental conditions within subjects was considered more valid than comparisons between subjects, the assumption that subjects were acting as their own controls in the former case may be in error. That is, as Grice (1966) aptly states,: " a subject who has served as his own control may not be the same subject that he would have been if he had not".

A common pattern of results to emerge within individuals was for placebo changes which were qualitatively and quantitatively similar to those demonstrated in the preceeding tryptophan phase. This outcome pattern was noted for both mood factor changes and side effect experience. Koch et al.'s (1983) demonstration that drug-placebo differences may be significantly affected by phase order suggests limitations on the validity of the present experiment due to the placebo - tryptophan order for 19/20 subjects. It is possible that psychological experience during the tryptophan period, combined with expectation of receiving tryptophan in both tablet phases, may have carried over in the form of expectancies to the placebo period - thus exaggerating phase similarities. Similarly the washout period may have been insufficient to avoid a pharmacological carry over of tryptophan effects to the placebo phase. While the effects of phase order

demand further investigation, the ignorance of tryptophan - placebo differences did not lead to any dramatic increase in the number or magnitude of significant relationships between tryptophan and baseline phases in the present experiment.

While significant levels of autocorrelation occurred frequently in the present data, reliance on the validity of statistical and visual analysis was generally limited to series free of this effect. The cautions employed in this respect undoubtedly contributed to a conservative interpretation of results.

A range of possibilities for the lack of therapeutic effects in the present investigation was put forward in the previous chapter. Such factors as the type or severity of depression, inappropriate dose levels, inadequate trial lengths, phase order, diet, insensitivity of scales or bias attributable to self rating procedures may all have contributed to the lack of response. A further potential contribution to the lack of therapeutic effect concerns the biochemical status of individuals classified as depressed. As mentioned in Chapter II, indices such as free plasma tryptophan concentration and the trp/5aa ratio are emerging as more powerful predictors than most psychological variables of therapeutic response to tryptophan administration (Moller et al., 1980). Knowledge of such parameters in the present investigation could have reduced the uncertainty associated with the cause of outcome in depressed subjects.

Despite the above limitations on the validity and generality of results, it seems fair to conclude that tryptophan is unlikely to possess dramatic and consistent mood altering effects across normal or depressed individuals. As discussed in the next sections, adequate investigation of tryptophan's psychological potential is considered to demand inclusion of physiological parameters (e.g. trp/5aa ratio) as independent variables.

5.2 THERAPEUTIC AND GENERAL MOOD ALTERING EFFECTS

The high level of conflict associated with purely psychological studies (discussed in the first part of Chapter II) was considered to reduce the importance of this information in the evaluation of relationships between tryptophan ingestion and psychological state. It was proposed that one source of controversy may be attributable to design and methodological differences between studies. Various inadequacies in this respect are also considered to reduce the validity of many psychological investigations.

Thus, the outcome from purely psychological studies was considered limited to indications of tryptophan's potential antidepressant value. While significant antidepressant effects have been repeatedly indicated, the level of efficacy relative to placebo, standard tricyclics or ECT remains controversial. In the context of potentiating effects, evidence is more consistently positive, indicating that tryptophan may possess significant therapeutic value in combination with the MAOI's. This indication also has reasonable theoretical support based on the presumed pharmacological actions of tryptophan and MAOI's described in Chapter II. Tryptophan's potentiating influence in conjunction with the tricyclics and ECT appears less promising on the basis of available evidence reviewed.

The limitation of significant psychological effects, in normal subjects, to principally negative states e.g. drowsiness and nausea (Charney et al., 1982; Greenwood et al., 1974; 1975; Smith & Prockop, 1962; Yuwiler et al., 1981), may be a consequence of focus of these inquiries on short term effects following acute tryptophan administration.

Methodological differences such as the psychological status of participants, dose level and duration of administration, between psychological studies were considered to inhibit valid comparison. The deviation of many studies from optimal dose levels and administration times (Chouinard et al., 1978) or the failure to investigate these parameters as independent variables was considered to restrict the validity of outcome for many

psychological trials.

Thus, purely psychological studies are not considered to provide an adequate evaluation of tryptophan's mood altering potential. The findings that antidepressant outcome may be significantly different between certain qualitative categories of depression e.g. bipolar versus unipolar classifications (Murphy et al., 1974; Farkas et al., 1976) indicates that tryptophan is unlikely to have a dramatic and uniform action across all psychological categories of depression.

Given the emergence of relationships between psychological state and biochemical indices of tryptophan metabolism, described in Chapter II, it became apparent that individual differences in such parameters may have contributed to the conflict and invalidity of outcome both between and within psychological studies.

Psychophysiological and psychopharmacological investigations of tryptophan were also considered to suffer methodological inadequacies similar to purely ~~the~~ psychological studies. Such factors have been raised and discussed in the last section of Chapter II. As with psychological investigations, the main criticism concerned the focus on between group differences, thus overlooking identification and analysis of individual responders.

Despite such limitations, reasonable evidence has emerged to support the value of free plasma tryptophan concentration and the trp/5aa ratio as meaningful correlates of antidepressant response in some cases, as well as providing a biochemical basis for discriminating between normal and depressed individiuals.

One of the few studies to have logically incorporated information on the psychophysiological relationships of tryptophan supports the speculation that employment of biochemical information may lead to a significant reduction in the uncertainty surrounding tryptophan's therapeutic value. Moller et al. (1980) demonstrated 80% remission after 14 days of tryptophan therapy in depressed patients selected for low tryp/5aa ratios. If the entire sample (which was heterogeneous

with respect to this parameter) had been considered then remission would only have been of the order of 28%. In the same study, a significantly high proportion of the bipolar depressives exhibited tryp/5aa ratios below the 15th percentile while no such pattern was apparent within unipolar depressives. Thus, the significantly superior therapeutic response demonstrated for bipolars versus unipolars (Murphy et al, 1974; Farkas et al., 1976; Moller et al., 1980) may relate to a higher representation of individuals with lower than normal tryp/5aa ratios.

Moller et al.'s (1980) investigation indicates the necessity of considering peripheral physiological indicators of tryptophan metabolism in order to accomplish a valid evaluation of its therapeutic potential. The possibility for a significant response in depressives with low free plasma concentrations, indicated in Chapter II, has not been so consistently endorsed. It seems probable that the tryp/5aa ratio may override the significance of free plasma tryptophan levels. That is, while free plasma concentrations appear to provide an index of brain tryptophan availability, it seems the amount of tryptophan that actually enters the brain will be finally dependent on the amount that can be carried. The trp/5aa ratio would seem to represent a closer indicator of this latter requirement.

Thus, it seems likely that investigation of the biochemical mechanisms proposed to intervene between tryptophan administration and altered psychological state (Figure 2-2), will significantly contribute to a valid evaluation of tryptophan's therapeutic potential.

5.3 TRYPTOPHAN'S POTENTIAL FOR INVESTIGATION OF SEROTONERGIC FUNCTION

Another potential area for tryptophan's utility concerns its value in determination of serotonin function. Understanding of tryptophan's psychopharmacological activity may also lead to a more informed evaluation of its mood altering potential and to possible refinements of its application in this context.

As indicated in Chapter II, past attempts at elucidating serotonin's psychobiochemical functions have involved investigation of the psychology and pharmacology of drugs assumed to alter serotonergic activity. On theoretical grounds, it is reasonable to assume that tryptophan may have some advantages over drugs such as LSD or reserpine which appear to significantly alter other neurotransmitter substances other as well as serotonin. Serotonin synthesis arising from tryptophan application should be selectively located within 5HT neurons due to the restriction of tryptophan hydroxylase to serotonergic neurons within the raphae system (Aghajanian & Wang, 1978). The use of tryptophan in this respect in humans is limited by uncertainty over whether application will result in sufficient elevation of brain tryptophan concentration. In addition, reliance on CSF 5HT-metabolite concentration as an indication of functional brain serotonin turnover may be in error as suggested by Grahame-Smith (1973) in Chapter II.

While it has been frequently assumed that the synthesis of brain serotonin is the most psychologically relevant effect of tryptophan administration, there is a need to further establish the psychological significance of other effects such as increased brain tryptamine, melatonin and nicotinic acid.

5.4 RECOMMENDATIONS FOR FUTURE RESEARCH

Conclusions relating to the present experiment and past investigations have been formulated with stated reservations regarding the adequacy of methods and relevance of the subjects studied. For this reason it is considered necessary to propose alternative research strategies which may avoid the criticism relevant to past studies.

The conflict emanating from purely psychological studies suggests that tryptophan administration is unlikely to possess generalized mood altering potential across different psychological groups or general antidepressant activity across psychologically and biochemically heterogenous groups of depressives. Progression from a review of purely psychological

studies to evaluation of trials including biochemical indices (e.g. free plasma tryptophan concentration and trp/5aa ratio) as a means of differentiating response indicated a positive but selective relevance for therapeutic tryptophan administration. Given that most therapeutic investigations, thus far, have failed to include biochemical information, the majority of past research is considered inadequate as a background for determination of tryptophan's antidepressant value. In addition, much past research was considered to be dependent on inappropriate design and methodological criteria. Consequently, it is considered that future research should be focused at methodological refinements for investigating the selective relevance of tryptophan's mood altering effects.

One of the most basic methodological requirements for valid evaluation of tryptophan's mood altering potential is seen as the need for within subject experimental and analysis procedures. There is a requirement for more specific psychological and biochemical identification of subjects in relation to outcome. Already, there is some evidence to support response difference between groups classified according to the polarity of depression (Farkas et al., 1976; Murphy et al., 1974; Moller et al., 1980). While significant relationships between severity of depression and therapeutic outcome have not yet been demonstrated, it was suggested in discussion of psychological studies that this variable may effect reaction to non specific e.g. environmental factors (Carroll, 1970), frequency of spontaneous remission or magnitude of the placebo effect (d'Elia et al., 1978). Thus, there is a need for further investigation of these relationships.

Moller et al.'s (1980) investigation has revealed more consistent promise for tryptophan's therapeutic efficacy in biochemically selected depressives. This finding concords with a proposed view of depression as "a biochemically heterogeneous group of disorders each requiring different treatment procedures to achieve maximal therapeutic effects" (Cotman & McGaugh, 1980). While there is evidence to suggest a significantly reduced turnover of CNS serotonin in some depressions (Coppen, et al. 1972; Asberg & Traskman, 1981; Bridges et al., 1976; Garelis, 1981; van Praag & Korf, 1970; Coppen, 1969; Aghajanian & Wang,

1978), CSF metabolites of serotonin do not offer a practical biochemical index for monitoring or screening in antidepressant trials. However, the peripheral plasma indicators - particulalry the trp/5aa ratio - have been demonstrated to correlate positively with CSF 5HIAA (Perez-Cruet et al.., 1974) and appear to be predictive of therapeutic outcome (Moller et al., 1980). Such indices, in contrast to CSF, metabolites represent acessible and routine parameters for sampling and analysis. Relationships between such biochemical indicators and psychological state need to considered with respect to extraneous variables such as diet composition, spacing of meals, time of day, season, age, weight to height relationships and sex which have all been shown to demonstrate significant associations with plasma tryptophan levels. Thus, further investigation is required to establish the value of the plasma tryptophan parameters as predictors of therapeutic outcome.

As is evident from the discussion of design for the present experiment, within subject approaches to pharmacological investigation tend to be more extravagent with time and clearly place greater demands on individual subjects. The need for all subjects to pass through all conditions also demands employing precautions such as washout periods between active drug and placebo phases and gaining awareness of the potential bias from factors such as phase order (Koch et al., 1983).

Although across subject recommendations regarding optimal therapeutic dose levels for tryptophan have been forwarded (Chouinard et al., 1978), reports of therapeutic efficacy have been claimed for doses well outside the recommended 6gms/day (Coppen et al., 1972). In addition, there seem to be logical reasons, e.g. differences in body weight and evidence indicating at least 15 fold differences in tricyclic dose requirements (Duquesne & Reeves, 1982) or thousand fold differences in nutrient requirements (Hoffer, 1974), to expect significant individual variation in therapeutic tryptophan requirements. Finally, Scoggins et al.'s (1976) estimations that 83% of interindividual variability in the plasma level of tricyclics could be attributed to individual metabolic differences, suggests the need for further investigations of dose level as an

independent variable within subjects. Further empirical investigation is also required to establish theoretical proposals that the psychopharmacological action of tryptophan will be enhanced by concomitant administration of tryptophan pyrrolase inhibitors and pyridoxine supplements.

Several theoretical and practical factors collaborate to suggest that administration in the form of a single nightly dose may be optimal. Given evidence for positive correlations between free plasma tryptophan levels and brain serotonin turnover (Curzon, 1981; Knott & Curzon, 1972; Young et al., 1976), Tagliamonte et al.'s (1974) report of free plasma tryptophan levels being 45% higher at midnight than at than at midday, suggest that the central process of tryptophan conversion to serotonin may be most active at night. Evidence from rat studies has also shown brain serotonin levels to peak at times of rest and to drop to their lowest during waking states (Luce, 1973). Other sources of evidence have indicated that the major catabolic pathway for tryptophan (kynurenine-anthranilate pathway) is least active at night (Curzon, 1969). Consequently, if the mechanism of action proposed (Figure 2-2) in this thesis is relevant it would seem that the psychological response to tryptophan administration should be improved with nightly administration due to increased activity of the serotonin pathway and reduced activity of the kynurenine pathway. Finally, the long biological half life of 15 hours reported for tryptophan (Ritschel, 1970) suggests that elevated plasma levels may be adequately maintained by a single nightly dose.

Other practical advantages of a single nightly dose include increased convenience for subjects having to remember only one ingestion time and the possibility of turning a frequently reported side effect of drowsiness shortly after ingestion (Yuwiler et al., 1981; Greenwood et al., 1974; 1975; Charney et al., 1982), to advantage (i.e. aiding sleep onset). Further investigation of the comparative efficacy of single versus two or three daily dose regimes within individuals is required.

The above recommendations for future reasearch into tryptophan's therapeutic potential are based on assumptions that

some depressive disorders may be associated with diminished serotonin turnover which may consequently be remedied through tryptophan loading. The relevance of such a procedure is logically limited to depressed individuals in the above category who do not exhibit abnormalities with respect to plasma-brain transport of tryptophan or other factors such as the enzymes required for serotonin synthesis. Similarly, such procedures would not be of relevance in depressions associated with abnormal elevations of tryptophan pyrrolase activity. Disorders in these latter respects are unlikely to be ammended through tryptophan loading and may account for therapeutic resistence in some subjects.

Tryptophan's level of efficacy and associated side effects relative to placebo and the tricyclics, needs to be clarified in order to assess its value in relation to standard medications. In this context there is a necessity to compare tryptophan with both placebo and active antidepressants within the same individuals. Clearly findings that tryptophan is not superior to placebo should not be taken as evidence for dismissal of tryptophan's antidepressant value. That is, several authors have failed, also, to demonstrate superiority of the tricyclics over placebo (Klerman & Cole, 1965; Raskin et al., 1970; Raskin, 1974; Morris & Beck, 1974).

As previously discussed, there is consistent evidence to support a more specific therapeutic role for tryptophan as a potentiating agent with MAOI's. Theoretical assumptions with respect to the action mechanisms of both substances support the expectation of synergistic psychopharmacological effects in this context. Further investigation is needed to determine the clinical significance of the improvement and to establish optimal dose levels for both compounds within individuals.

As was mentioned in Chapter II, several investigations have been undertaken to determine relationships between tryptophan administration and various sleep parameters. It was not the intention of the present thesis to review this area of application in detail. However, there are indications that future research in this area may establish another locus of therapeutic

potential for tryptophan administration. That is, a review of 8 studies in this area by Cooper (1979), supported overall findings of significantly reduced sleep latency and increase in total sleep time as well as trends towards improved subjective quality of sleep.

Although self rating methods of psychological assessment were promoted in the present investigation, there are certain contexts e.g. in cases of severe depression, where expectation of subjects to conduct reliabale self assessment may be inapproriate. In this respect, it is considered desirable that other rater scales should be included in addtion to self rating procedures. Other recommendations for scales suitable in the detection of tryptophan effects have been discussed in detail in Chapter III.

The value of future research on tryptophan intake in normal subjects is less certain than that of therapeutically oriented evaluations. As noted in Chapter II, most investigations with normal subjects involved short term monitoring of mood and side effects following single doses of tryptophan. There is a need for further investigation of chronic tryptophan administration in normal subjects before the psychoactive properties of tryptophan in this group can be established. It is not considered that normal subjects should be employed as models for investigation of antidepressant effects. However, normal subjects may have relevance in studies of depression if the point of inquiry is to specifically investigate hypotheses that depression is simply an extension of normal downward mood swings.

Another reason for continued investigation of tryptophan's effects in populations free of psychiatric disturbance is the provision of scientific information which may aid the decisions of potential consumers. This area of investigation is of particular relevance within New Zealand where tryptophan availability is unrestricted. While it is seen as desirable for individuals to formulate their own judgements with respect to tryptophan's efficacy it is also considered expedient to increase the availability of unbiased evidence regarding its psychotropic potential.

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APPENDIX A

PSYCHOLOGICAL SCALES USED IN THE PRESENT THESIS

I. Demographic questionnaire
II. Morning Moodscale
III. Evening Moodscale
IV. Side effect checklist
V. Zung Depression Scale
VI. Trait Anxiety Scale
VII. State Anxiety Scale
VIII. Hopkins Symptom Check List (HSCL)

(all scales are reduced to 3/4 of the original size)

I. Demographic questionnaire

PLEASE RESPOND TO ALL QUESTIONS - ALL INFORMATION WILL REMAIN STRICTLY CONFIDENTIAL.

NAME: _____ ID: _____
(surname) (firstname)

PHONE: HOME: _____
POSTAL ADDRESS: _____
WORK: _____

(1)AGE: _____ (2)SEX: _____ (3)HEIGHT: _____ (4)WEIGHT: _____

(5)MARITAL STATUS:
(tick appropriate space)

single ____
defacto ____
married ____
divorced ____
separated ____
widowed ____

(6)LIVING SITUATION:
(tick all applicable)

alone ____
sharing others(excl spouse) ____
with spouse ____
with parents ____
with children ____
other(specify): _____

(7)EDUCATION LEVEL:
(tick highest applicable)

primary ____
4th form ____
school cert. ____
U.E. ____
Tech. qualification ____
University degree ____
other(specify) _____

(8)OCCUPATION:
(tick all applicable)

student ____
paid employment ____
unemployed(regist) ____
homemaker ____
retired ____

(9)MEDICAL/PSYCHOLOGICAL CONDITIONS:
(tick all applicable)

diabetes ____
anorexia nervosa ____
bulimia ____
alcoholic problems ____
other(specify) _____

(10)DRUG CONSUMPTION: - in the last month -
(tick all applicable)

	reg	occas	not all
antidepressants	____	____	____
analgesics/painkillers	____	____	____
antipsychotics	____	____	____
tranquillizers/sleeping pills	____	____	____
psychedelics/marijuana	____	____	____
diet medication	____	____	____
vitamin supplements	____	____	____
specify: _____			
other	____	____	____
specify: _____			

(11)Do you consider you are likely to be/come a regular/occasional consumer of any of the above in the next 6 months? Yes____ No____

(12)PSYCHOTHERAPY: - in last month -
(tick all applicable)

behaviour modification ____
ECT ____
indiv/group psychotherapy ____
other(specify) _____

(13)Do you consider it likely that you will partake of any of the above in the next 6 months? Yes____ No____

(14)IF FEMALE ARE/DO YOU:

	Yes	No
pregnant	___	___
take chemical contraceptives	___	___
suffer premenstrual tension	___	___

(15)L-TRYTOPHAN CONSUMPTION

Have you consumed L-Tryptophan tablets:	Yes	No
- before	___	___
- in the last month	___	___

If Yes in last month please specify how much _____

In either case did you notice any change in the way you felt - please specify: _____

(16)ARE YOU VEGETARIAN? Yes____ No____

(17)Were there any questions you did not answer for personal reasons: Yes____ No____

- please specify numbers: _____

II. Morning Moodscale

Morning Mood scale - all information will remain strictly confidential

Day + date: _____ Time: _____ ID: _____

How many hours of sleep did you have last night? _____

If female - are you menstruating? Yes: ___ No: ___

Has anything unusual/traumatic happened since you completed the last scale to make you feel very different from normal? Yes: ___ No: ___

please specify: _____

_____

Have you consumed any drugs since completing the last scale? Yes: __ No: __

please specify types & dose: _____

_____

(1)Please rate your subjective state in terms of the dimensions given below.
(2)Regard the adjectives as representing the extreme condition. For example, one is seldom absolutely "Honest" or Dishonest", normally honesty would be rated in the mid range of the line.
(3)Deal with one dimension at a time, expressing how you feel at the moment.
(4)Mark clearly and perpendicularly across each line.

Alert	_____	Drowsy
Calm	_____	Excited
Strong	_____	Feeble
Muzzy	_____	Clear-headed
Well-coordinated	_____	Clumsy
Lethargic	_____	Energetic
Contented	_____	Discontented
Troubled	_____	Tranquil
Mentally slow	_____	Quick-witted
Tense	_____	Relaxed
Attentive	_____	Dreamy
Incompetent	_____	Proficient
Happy	_____	Sad
Antagonistic	_____	Amicable
Interested	_____	Bored
Withdrawn	_____	Gregarious

III. Evening Moodscale

Evening Mood scale - all information will remain strictly confidential

Day + date: _____ Time: _____ ID: _____

If female - are you menstruating? Yes: ___ No: ___

Has anything unusual/traumatic happened since you completed the last scale to make you feel very different from normal? Yes: ___ No: ___

please specify: _____

_____

---

(1)Please rate your subjective state in terms of the dimensions given below.
(2)Regard the adjectives as representing the extreme condition. For example, one is seldom absolutely "Honest" or Dishonest", normally honesty would be rated in the mid range of the line.
(3)Deal with one dimension at a time, expressing how you feel at the moment.
(4)Mark clearly and perpendicularly across each line.

Alert	_____	Drowsy
Calm	_____	Excited
Strong	_____	Feeble
Muzzy	_____	Clear-headed
Well-coordinated	_____	Clumsy
Lethargic	_____	Energetic
Contented	_____	Discontented
Troubled	_____	Tranquil
Mentally slow	_____	Quick-witted
Tense	_____	Relaxed
Attentive	_____	Dreamy
Incompetent	_____	Proficient
Happy	_____	Sad
Antagonistic	_____	Amicable
Interested	_____	Bored
Withdrawn	_____	Gregarious

PTO.....

IV. Side effect checklist

TICK THE FOLLOWING ONLY IF THEY AFFECT/ED YOU TODAY:

	a little	quite a bit	extreme
1. Headache.....	_____	_____	_____
2. Nausea/vomitting.....	_____	_____	_____
3. Blurred vision.....	_____	_____	_____
4. Constipation.....	_____	_____	_____
5. Diarrhoea.....	_____	_____	_____
6. Dry mouth.....	_____	_____	_____
7. Urinary retention.....	_____	_____	_____
8. Increased appetite.....	_____	_____	_____
9. Decreased appetite.....	_____	_____	_____
10. Dizziness.....	_____	_____	_____
11. Sweating.....	_____	_____	_____

please specify any other symptoms: _____

_____

_____

V. Zung Depression Scale

ZUNG

ID: _____ DATE: _____

Listed below are 20 statements. Please read each one carefully and decide how much of the statement describes how you have been feeling during the past week. Decide whether the statement applies to you for none or a little of the time, some of the time, a good part of the time, or most or all of the time. Tick the appropriate column for each statement.

		None or a little of the time	Some of the time	A good part of the time	Most or all of the time
1.	I feel downhearted and blue.....	_____	_____	_____	_____
2.	Morning is when I feel the best..	_____	_____	_____	_____
3.	I have crying spells or feel like it.....	_____	_____	_____	_____
4.	I have trouble sleeping through the night.....	_____	_____	_____	_____
5.	I eat as much as I used to.....	_____	_____	_____	_____
6.	I enjoy looking at, talking to and being with attractive women (or men).....	_____	_____	_____	_____
7.	I notice that I am losing weight	_____	_____	_____	_____
8.	I have trouble with constipation	_____	_____	_____	_____
9.	My heart beats faster than usual	_____	_____	_____	_____
10.	I get tired for no reason.....	_____	_____	_____	_____
11.	My mind is as clear as it used to be.....	_____	_____	_____	_____
12.	I find it easy to do the things I used to.....	_____	_____	_____	_____
13.	I am restless and can't keep still	_____	_____	_____	_____
14.	I feel hopeful about the future..	_____	_____	_____	_____
15.	I am more irritable than usual...	_____	_____	_____	_____
16.	I find it easy to make decisions	_____	_____	_____	_____
17.	I feel that I am useful and needed	_____	_____	_____	_____
18.	My life is pretty full.....	_____	_____	_____	_____
19.	I feel that others would be better off if I were dead.....	_____	_____	_____	_____
20.	I still enjoy the things I used to	_____	_____	_____	_____

PTO.....

VI. Trait Anxiety Scale

SELF-EVALUATION QUESTIONNAIRE (2)

ID: _____ DATE: _____

Directions: A number of statements which people have used to describe themselves are given below. Read each statement and then tick the appropriate space to the right of the statement to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	Not at all	Somewhat	Moderately so	Very much so
21. I feel pleasant.....	_____	_____	_____	_____
22. I tire quickly.....	_____	_____	_____	_____
23. I feel like crying.....	_____	_____	_____	_____
24. I wish I could be as happy as others seem to be.....	_____	_____	_____	_____
25. I am losing out on things because I can't make up my mind soon enough...	_____	_____	_____	_____
26. I feel rested.....	_____	_____	_____	_____
27. I am "calm, cool and collected".....	_____	_____	_____	_____
28. I feel that difficulties are piling up so that I cannot overcome them...	_____	_____	_____	_____
29. I worry too much over something that really doesn't matter.....	_____	_____	_____	_____
30. I am happy.....	_____	_____	_____	_____
31. I am inclined to take things hard...	_____	_____	_____	_____
32. I lack self-confidence.....	_____	_____	_____	_____
33. I feel secure.....	_____	_____	_____	_____
34. I try to avoid facing a crisis or difficulty.....	_____	_____	_____	_____
35. I feel blue.....	_____	_____	_____	_____
36. I am content.....	_____	_____	_____	_____
37. Some unimportant thought runs through my mind and bothers me.....	_____	_____	_____	_____
38. I take disappointments so keenly that I can't put them out of my mind.....	_____	_____	_____	_____
39. I am a steady person.....	_____	_____	_____	_____
40. I get in a state of tension or turmoil as I think over my recent concerns and interests.....	_____	_____	_____	_____

VII. State Anxiety Scale

SELF-EVALUATION QUESTIONNAIRE (1)

ID: _____ DATE: _____

Directions: A number of statements which people have used to describe themselves are given below. Read each statement and then tick the appropriate space to the right of the statement to indicate how you feel right now, that is at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
1. I feel calm.....	_____	_____	_____	_____
2. I feel secure.....	_____	_____	_____	_____
3. I am tense.....	_____	_____	_____	_____
4. I am regretful.....	_____	_____	_____	_____
5. I feel at ease.....	_____	_____	_____	_____
6. I feel upset.....	_____	_____	_____	_____
7. I am presently worrying over possible misfortunes.....	_____	_____	_____	_____
8. I feel rested.....	_____	_____	_____	_____
9. I feel anxious.....	_____	_____	_____	_____
10. I feel comfortable.....	_____	_____	_____	_____
11. I feel self-confident.....	_____	_____	_____	_____
12. I feel nervous.....	_____	_____	_____	_____
13. I am jittery.....	_____	_____	_____	_____
14. I feel "high strung".....	_____	_____	_____	_____
15. I am relaxed.....	_____	_____	_____	_____
16. I feel content.....	_____	_____	_____	_____
17. I am worried.....	_____	_____	_____	_____
18. I feel overexcited and "rattled"....	_____	_____	_____	_____
19. I feel joyful.....	_____	_____	_____	_____
20. I feel pleasant.....	_____	_____	_____	_____

VIII. Hopkins Symptom Check List (HSCL)

SYMPTOM CHECKLIST

Below is a list of problems and complaints that people sometimes have. Please read each one carefully. After you have done so, please tick only one of the four spaces to the right that best describes HOW MUCH THAT PROBLEM HAS BOTHERED OR DISTRESSED YOU DURING THE PAST WEEK, INCLUDING TODAY. Make only one tick for each problem and do not skip any items.

**ID:_____ DATE:_____ WEIGHT:_____

	Not at all	A little	Quite a bit	Extremely
1. Headaches.....	_____	_____	_____	_____
2. Nervousness or shaking inside.....	_____	_____	_____	_____
3. Being unable to get rid of bad thoughts/ideas	_____	_____	_____	_____
4. Faintness of dizziness.....	_____	_____	_____	_____
5. Loss of sexual interest or pleasure.....	_____	_____	_____	_____
6. Feeling critical of others.....	_____	_____	_____	_____
7. Bad dreams.....	_____	_____	_____	_____
8. Difficulty in speaking when you are excited	_____	_____	_____	_____
9. Trouble remembering things.....	_____	_____	_____	_____
10. Worried about sloppiness or carelessness....	_____	_____	_____	_____
11. Feeling easily annoyed or irritated.....	_____	_____	_____	_____
12. Pains in the heart or chest.....	_____	_____	_____	_____
13. Itching.....	_____	_____	_____	_____
14. Feeling low in energy or slowed down.....	_____	_____	_____	_____
15. Thoughts of ending your life.....	_____	_____	_____	_____
16. Sweating.....	_____	_____	_____	_____
17. Trembling.....	_____	_____	_____	_____
18. Feeling confused.....	_____	_____	_____	_____
19. Poor appetite.....	_____	_____	_____	_____
20. Crying easily.....	_____	_____	_____	_____
21. Feeling shy or uneasy with the opposite sex	_____	_____	_____	_____
22. A feeling of being trapped or caught.....	_____	_____	_____	_____
23. Suddenly scared for no reason.....	_____	_____	_____	_____
24. Temper outbursts you could not control.....	_____	_____	_____	_____
25. Constipation.....	_____	_____	_____	_____
26. Blaming yourself for things.....	_____	_____	_____	_____
27. Pains in the lower part of your back.....	_____	_____	_____	_____
28. Feeling blocked or stymied in getting things done.....	_____	_____	_____	_____

PTO.....

	Not at all	A little	Quite a bit	Extremely
29. Feeling lonely.....	_____	_____	_____	_____
30. Feeling blue.....	_____	_____	_____	_____
31. Worrying or stewing about things.....	_____	_____	_____	_____
32. Feeling no interest in things.....	_____	_____	_____	_____
33. Feeling fearful.....	_____	_____	_____	_____
34. Your feelings being easily hurt.....	_____	_____	_____	_____
35. Having to ask others what you should do.....	_____	_____	_____	_____
36. Feeling others do not understand you or are unsympathetic.....	_____	_____	_____	_____
37. Feeling that people are unfriendly or dislike you.....	_____	_____	_____	_____
38. Having to do things very slowly in order to be sure you were doing them right.....	_____	_____	_____	_____
39. Heart pounding or racing.....	_____	_____	_____	_____
40. Nausea or upset stomach.....	_____	_____	_____	_____
41. Feeling inferior to others.....	_____	_____	_____	_____
42. Soreness of your muscles.....	_____	_____	_____	_____
43. Loose bowel movements.....	_____	_____	_____	_____
44. Difficulty in falling asleep/staying asleep	_____	_____	_____	_____
45. Having to check and double check what you do	_____	_____	_____	_____
46. Difficulty making decisions.....	_____	_____	_____	_____
47. Wanting to be alone.....	_____	_____	_____	_____
48. Trouble getting your breath.....	_____	_____	_____	_____
49. Hot or cold spells.....	_____	_____	_____	_____
50. Having to avoid certain things, places or activities because they frighten you.....	_____	_____	_____	_____
51. Your mind going blank.....	_____	_____	_____	_____
52. Numbness or tingling in parts of your body..	_____	_____	_____	_____
53. A lump in your throat.....	_____	_____	_____	_____
54. Feeling hopeless about the future.....	_____	_____	_____	_____
55. Trouble concentrating.....	_____	_____	_____	_____
56. Weakness in parts of your body.....	_____	_____	_____	_____
57. Feeling tense or keyed up.....	_____	_____	_____	_____
58. Heavy feeling in your arms or legs.....	_____	_____	_____	_____

APPENDIX B

COMPUTER PROGRAM LISTINGS USED FOR ANALYSIS IN THE PRESENT THESIS

I. Factor extraction program for VAMS

II. Autocorrelation program

III. C statistic program

IV. Factor extraction program for HSCL

I. Factor extraction program for VAMS

The following program outputs factor scores for three mood dimensions: alertness, contentedness and calmness, using factor loadings from Bond & Lader (1974). Input is in the form of mood scores for the 16 scales (see VAMS: Appendix A). The program also outputs factor score means for experimental phases relevant to each subject.

```
      INTEGER I,J,K,L,M,N,ID,RSCORE(84,16),FACTOR(84,3)
      INTEGER ILOAD(16),IREV(16)
      INTEGER IBL1,ITL,IWL,IPL,IBL2,ITLD,IWLD,IPLD,T
      REAL LOAD(16),CMPSCR(84,16),BASTOT,TRPTOT,WSHTOT,BS2TOT
      REAL BSEMN1,BSEMN2,BSEMN3,TREMN1,TREMN2,TREMN3,WSHMN1
      REAL WSHMN2,WSHMN3,PLCMN1,PLCMN2,PLCMN3,BS2MN1,BS2MN2,BS2MN3
      REAL BL1,TL,WL,PL,BL2,ALOAD1,ALOAD2,ALOAD3,ACMPS1,ACMPS2,ACMPS3
      WRITE(1,60)
   60 FORMAT(5X,'SUBJECTS ID: ',/,5X,'TOT NO EXP DAYS: ',/,5X,'NO BASE1
     6 DAYS: ',/,5X,'NO TRYP DAYS: ',/,5X,'NO WSH DAYS: ',/,5X,'NO PLCB
     6 DAYS: ',/,5X,'NO BASE2 DAYS: ')
      READ(1,50) ID,N,BL1,TL,WL,PL,BL2
   50 FORMAT(2(I2,/),5(F2.0,/))
      WRITE(1,61)
   61 FORMAT(5X,'MORNING (1)/EVENING (2): ')
      READ(1,51)T
   51 FORMAT(I1)
      IBL1=IFIX(BL1)
      ITL=IFIX(TL)
      IWL=IFIX(WL)
      IPL=IFIX(PL)
      IBL2=IFIX(BL2)
      OPEN(UNIT = 6,FILE = 'RSCORE',STATUS = 'OLD')
      DO 1 I=1,N
    1 READ(6,10) (RSCORE(I,J),J=1,16)
   10 FORMAT(16(I3))
      CLOSE(UNIT = 6)
      OPEN(UNIT = 6,FILE = 'LOAD',STATUS = 'OLD')
      READ(6,20) (ILOAD(K),K=1,16)
   20 FORMAT(16(I4))
      CLOSE(UNIT = 6)
      OPEN(UNIT = 6,FILE = 'IREV',STATUS = 'OLD')
      READ(6,23) (IREV(M),M=1,16)
   23 FORMAT(16(I2))
      CLOSE(UNIT = 6)
      OPEN(UNIT = 6,FILE = 'FACTOR',STATUS = 'NEW')
      DO 3 L=1,N
      DO 7 I=1,16
    7 LOAD(I)=FLOAT(ILOAD(I))/1000.0
      DO 4 M=1,16
      IF((RSCORE(L,M)).EQ.99) LOAD(M)=0.00
      IF((RSCORE(L,M)).EQ.-1) RSCORE(L,M)=100
      IF(IREV(M).EQ.1) RSCORE(L,M)=100-RSCORE(L,M)
      IF((RSCORE(L,M)).EQ.00) RSCORE(L,M)=01
    4 CMPSCR(L,M)=RSCORE(L,M)*LOAD(M)
     ALOAD1=LOAD(1)+LOAD(11)+LOAD(6)+LOAD(4)+LOAD(5)+LOAD(9)+
     6LOAD(3)+LOAD(15)+LOAD(12)
      IF(ALOAD1 .EQ. 0.00) GO TO 110
     ACMPS1=CMPSCR(L,1)+CMPSCR(L,11)+CMPSCR(L,6)+CMPSCR(L,4)
     6+CMPSCR(L,5)+CMPSCR(L,9)+CMPSCR(L,3)+CMPSCR(L,15)+CMPSCR(L,12)
      FACTOR(L,1)=IFIX(ACMPS1/ALOAD1)
      GO TO 120
```

```
110 FACTOR(L,1)=0
120 ALOAD2=LOAD(13)+LOAD(14)+LOAD(8)+LOAD(7)+LOAD(16)
    IF(ALOAD2 .EQ. 0.00) GO TO 210
    ACMPS2=CMPSCR(L,13)+CMPSCR(L,14)+CMPSCR(L,8)+CMPSCR(L,7)
   6+CMPSCR(L,16)
    FACTOR(L,2)=IFIX(ACMPS2/ALOAD2)
    GO TO 220
210 FACTOR(L,2)=0
220 ALOAD3=LOAD(2)+LOAD(10)
    IF(ALOAD3 .EQ. 0.00) GO TO 310
    ACMPS3=CMPSCR(L,2)+CMPSCR(L,10)
    FACTOR(L,3)=IFIX(ACMPS3/ALOAD3)
     GO TO 3
310  FACTOR(L,3)=0
  3 CONTINUE
     DO 5 J=1,3
     BASIOI=0.0
     TRPIOI=0.0
     WSHIOI=0.0
     PLCIOI=0.0
     BS2IOI=0.0
     DO 6 I=1,IBL1
  6 BASIOI=BASIOI+FACTOR(I,J)
    ITLD=IBL1+ITL
     DO 8 I=IBL1+1,ITLD
  8 TRPIOI=TRPIOI+FACTOR(I,J)
    IWLD=ITLD+IWL
     DO 9 I=ITLD+1,IWLD
  9 WSHIOI=WSHIOI+FACTOR(I,J)
    IPLD=IWLD+IPL
     DO 13 I=IWLD+1,IPLD
 13 PLCIOI=PLCIOI+FACTOR(I,J)
     DO 15 I=IPLD+1,N
 15 BS2IOI=BS2IOI+FACTOR(I,J)
     IF (J.EQ.1) GO TO 100
     IF (J.EQ.2) GO TO 200
     IF (J.EQ.3) GO TO 300
100 BSEMN1=BASIOI/BL1
     TRPMN1=TRPIOI/TL
     WSHMN1=WSHIOI/WL
     PLCMN1=PLCIOI/PL
     BS2MN1=BS2IOI/BL2
200 BSEMN2=BASIOI/BL1
     TRPMN2=TRPIOI/TL
     WSHMN2=WSHIOI/WL
     PLCMN2=PLCIOI/PL
     BS2MN2=BS2IOI/BL2
300 BSEMN3=BASIOI/BL1
     TRPMN3=TRPIOI/TL
     WSHMN3=WSHIOI/WL
     PLCMN3=PLCIOI/PL
     BS2MN3=BS2IOI/BL2
  5 CONTINUE
    IF(T.EQ.1) GO TO 401
    IF(T.EQ.2) GO TO 400
400  WRITE(6,500)
```

```
500   FORMAT(5X,'EVENING DATA')
      GO TO 600
401   WRITE(6,501)
501   FORMAT(5X,'MORNING DATA')
 600  WRITE(6,33) ID
  33  FORMAT(/,'SUBJECT NO: ',I2)
      WRITE(6,35)N
  35  FORMAT(///,'TOTAL NO. DAYS: ',I2)
      WRITE(6,83)BL1,TL,WL,PL,BL2
  83  FORMAT(/,5X,'BASELINE1 = ',F5.2,/,5X,'TRYPTOPHAN = ',F5.2,/,5X,
     6'WASHOUT = ',F5.2,/,5X,'PLACEBO = ',F5.2,/,5X,'BASELINE2 = ',F5.2)
        DO 14 J=1,3
        WRITE(6,30)J
  30  FORMAT(//,10X,'FACTOR',I1)
        WRITE(6,40) (FACTOR(I,J),I=1,26)
        WRITE(6,40) (FACTOR(I,J),I=27,52)
        WRITE(6,40) (FACTOR(I,J),I=53,78)
        WRITE(6,40) (FACTOR(I,J),I=79,84)
  40  FORMAT(26(I3))
  14  CONTINUE
        WRITE(6,80)1,BSEMN1,TRPMN1,WSHMN1,PLCMN1,BS2MN1
        WRITE(6,81)2,BSEMN2,TRPMN2,WSHMN2,PLCMN2,BS2MN2
        WRITE(6,82)3,BSEMN3,TRPMN3,WSHMN3,PLCMN3,BS2MN3
  80  FORMAT(///,'FACTOR ',I1,3X,' BASEMEAN1 =',F6.3,' TRYPMEAN =',F6.3,
     6' WSHIMEAN1 =',F6.3,/,11X,' PLCBMEAN1 =',F6.3,' BAS2MEAN1 =',F6.3)
  81  FORMAT(/,'FACTOR ',I1,3X,' BASEMEAN2 =',F6.3,' TRYPMEAN2 =',F6.3,
     6' WSHIMEAN2 =',F6.3,/,11X,' PLCBMEAN2 =',F6.3,' BAS2MEAN2 =',F6.3)
  82  FORMAT(/,'FACTOR ',I1,3X,' BASEMEAN3 =',F6.3,' TRYPMEAN3 =',F6.3,
     6' WSHIMEAN3 =',F6.3,/,11X,' PLCBMEAN3 =',F6.3,' BAS2MEAN3 =',F6.3)
        CLOSE(UNIT = 6)
        END
```

II. Autocorrelation program

The following fortran program listing includes the computational proceedures designed according to the formula:

$$r_k = \sum_{i=1}^{N-k} (Z_i - Z)(Z_{i+k} - Z) \Big/ \sum_{i=1}^{N} (Z_i - Z)^2$$

Where: N is the total number of observations in the series, Z_i is the value of the observation at time period i, Z is the mean of the series and k is the number of lags.

The program outputs the raw data and associated r_k scores (k=lag1,lag4) for input series up to 100 points:

```
      PROGRAM AUTCOR
      INTEGER SERIS(100),N,I,J,L,M,P,S,Q
      REAL ZMEAN,T,RN,ZN,ZD,R1,R2,R3,R4
      WRITE(1,11)
   11 FORMAT(5X,'ENTER LENGTH OF SERIES:  ')
      READ(1,10)N
   10 FORMAT(I3)
      T = 0.0
      ZN = 0.0
      ZD = 0.0
      CALL OPEN (6,'SERIS   DAT',0)
      DO 1 I=1,N
    1 READ(6,20)SERIS(I)
   20 FORMAT(I2)
      ENDFILE 6
      DO 2 J=1,N
    2 T=T+SERIS(J)
      RN=FLOAT(N)
      ZMEAN=T/RN
      DO 3 L=1,N
    3 ZD=ZD+((SERIS(L)-ZMEAN)**2)
      DO 4 M=1,4
      S=N-M
      DO 5 P=1,S
      Q = P+M
      ZN=ZN+((SERIS(P)-ZMEAN)*(SERIS(Q)-ZMEAN))
    5 CONTINUE
      IF(M.EQ.1)R1=ZN/ZD
      IF(M.EQ.2)R2=ZN/ZD
      IF(M.EQ.3)R3=ZN/ZD
      IF(M.EQ.4)R4=ZN/ZD
      ZN=0.0
    4 CONTINUE
      CALL OPEN (6,'RANSWER DAT',0)
      WRITE(1,21)
      WRITE(6,21)
   21 FORMAT(//,5X,'data seris: ')
      WRITE(1,31)(SERIS(I), I=1,N)
      WRITE(6,31)(SERIS(I), I=1,N)
   31 FORMAT(/,5(20I3,/))
      WRITE(1,41)
      WRITE(6,41)
   41 FORMAT(//,5x,'autocorrelations (lags 1-4): ')
      WRITE(1,51)R1,R2,R3,R4
```

```
      WRITE(6,51)R1,R2,R3,R4
   51 FORMAT(/,5X,'r1 = 'F12.10,/,5X,'r2 = 'F12.10,/,5X,'r3 = '
     6F12.10,/,5X,'r4 = 'F12.10)
      ENDFILE 6
      END
```

III. C statistic program

The following program outputs the data series understudy, the associated C (C statistic), SC (standard error of C) and Z (Z statistic, ie: ratio of C to SC).

```
       PROGRAM CSTAT
C
C - outputs values for:  C statistic (C)
C                        standard error of C (Sc)
C                        Z statistic ie: ratio of C to Sc (Z)
C     - for specified no. of data points (N)
C
      INTEGER  I,J,K,L,N,LN,ID,SER,PHS,FAC,TSCORE(120)
      INTEGER  CANS(50,50)
      REAL  MEAN,MS,MSx2,DS,T,C,SC,Z,RN
      T=0.0
      MS=0.0
      DS=0.0
      WRITE(1,60)
   60 FORMAT(8X,'SUBJECT NO? : ')
      READ(1,9)ID
    9 FORMAT(I2)
      WRITE(1,80)
   80 FORMAT(//,8X,'ENTER SERIES NO.:',/,8X,'morning(1):
     6 evening(2): combined(3): ')
      READ(1,13)SER
   13 FORMAT(I1)
      WRITE(1,18)
   18 FORMAT(//,8X,'ENTER PHASE:',/,8X,'baseline(1):
     6tryptophan(2): washout(3): placebo(4): base2(5):'/,8X,
     6'mianserin(6): tryp2(7): baseline+tryptophan(8):',/,8X,
     6'tryptophan+placebo(9): placebo 6+base2(10):')
      READ(1,19)PHS
   19 FORMAT(I2)
      WRITE(1,16)
   16 FORMAT(//,8X,'ENTER MOOD FACTOR: ',/,8X,'alertness(1):
     6 contentedness(2): calmness(3): ')
      READ(1,17)FAC
   17 FORMAT(I1)
      WRITE (1,11)
11    FORMAT(///, 5X,'NO OF DATA POINTS?: ')
      READ(1,10)N
10    FORMAT(I3)
      CALL OPEN (6,'TSCORE  DAT',0)
C     READ DATA
      DO 1 I = 1,N
 1    READ(6,20)TSCORE(I)
20    FORMAT(I3)
      ENDFILE 6
C     CALCULATE SUM OF (N) DATA POINTS (T)
      DO 2 J = 1,N
 2    T = T + TSCORE(J)
```

```
      RN = FLOAT(N)
C     CALCULATE MEAN OF DATA POINTS
      MEAN = T/RN
C     CALCULATE 2xSUM OF (N) SQUARED DEVIATIONS FROM THEIR
C     MEAN (MS)
      DO 3 K = 1,N
 3    MS = MS + (TSCORE(K)-MEAN)**2
      LN = N-1
C     CALCULATE (N-1) SQUARED CONSECUTIVE DIFFERENCES (DS)
      DO 4 L = 1,LN
 4    DS = DS + (TSCORE(L)-(TSCORE(L+1)))**2
      C = 1 - (DS/(2*MS))
      MSx2 = MS*2
      SC = SQRT((RN-2)/((RN-1)*(RN+1)))
      Z = C/SC
C     OUTPUT - C, Sc and Z:
      CALL OPEN(6,'CANS    DAT',0)
      WRITE(6,41)ID
      WRITE(1,41)ID
   41 FORMAT(5X,'SUBJECT:',I2)
      IF (SER .EQ. 1) GO TO 100
      IF (SER .EQ. 2) GO TO 200
      IF (S ER .EQ. 3) GO TO 300
 100  WRITE(1,110)
      WRITE(6,110)
 110  FORMAT(/,5X,'TIME SERIS: morning')
      GO TO 800
 200  WRITE(1,210)
      WRITE(6,210)
 210  FORMAT(/,5X,'TIME SERIS: evening')
      GO TO 800
 300  WRITE(1,310)
      WRITE(6,310)
 310  FORMAT(/,5X,'TIME SERIS: combined morn + eve data')
 800  IF (PHS .EQ. 1) GO TO 1000
      IF (PHS .EQ. 2) GO TO 2000
      IF (PHS .EQ. 3) GO TO 3000
      IF (PHS .EQ. 4) GO TO 4000
      IF (PHS .EQ. 5) GO TO 5000
      IF (PHS .EQ. 6) GO TO 6000
      IF (PHS .EQ. 7) GO TO 7000
      IF (PHS .EQ. 8) GO TO 8000
      IF (PHS .EQ. 9) GO TO 9000
      IF (PHS .EQ. 10)GO TO 10000
1000  WRITE(1,1010)
      WRITE(6,1010)
1010  FORMAT(5X,'PHASE: baseline 1')
      GO TO 900
2000  WRITE(1,2010)
      WRITE(6,2010)
2010  FORMAT(5X,'PHASE: tryptophan')
      GO TO 900
3000  WRITE(1,3010)
      WRITE(6,3010)
3010  FORMAT(5X,'PHASE: washout')
      GO TO 900
4000  WRITE(1,4010)
      WRITE(6,4010)
4010  FORMAT(5X,'PHASE: placebo')
      GO TO 900
```

```
5000  WRITE(1,5010)
      WRITE(6,5010)
5010  FORMAT(5X,'PHASE: base 2')
      GO TO 900
6000  WRITE(1,6010)
      WRITE(6,6010)
6010  FORMAT(5X,'PHASE: mianserin')
      GO TO 900
7000  WRITE(1,7010)
      WRITE(6,7010)
7010  FORMAT(5X,'PHASE: tryp2')
      GO TO 900
8000  WRITE(1,8010)
      WRITE(6,8010)
8010  FORMAT(5X,'PHASE: baseline 1 + tryptophan ')
      GO TO 900
9000  WRITE(1,9010)
      WRITE(6,9010)
9010  FORMAT(5X,'PHASE: tryptophan + placebo ')
      GO TO 900
10000 WRITE(1,10010)
      WRITE(6,10010)
10010 FORMAT(5X,'PHASE: placebo + base2 ')
 900  IF (FAC .EQ. 1) GO TO 1111
      IF (FAC .EQ. 2) GO TO 2222
      IF (FAC .EQ. 3) GO TO 3333
1111  WRITE(1,1110)
      WRITE(6,1110)
1110  FORMAT(5X,'MOOD FACTOR: alertness')
      GO TO 600
2222  WRITE(1,2220)
      WRITE(6,2220)
2220  FORMAT(5X,'MOOD FACTOR: contentedness')
      GO TO 600
3333  WRITE(1,3330)
      WRITE(6,3330)
3330  FORMAT(5X,'MOOD FACTOR: calmness')
 600  WRITE(6,31)(TSCORE(I),I=1,N)
      WRITE(1,31)(TSCORE(I),I=1,N)
31    FORMAT(/,4X,5(2OI3,/,4X))
      WRITE(6,21)C,DS,MSx2,SC,Z
      WRITE(1,21)C,DS,MSx2,SC,Z
21    FORMAT(///,5X,'C = 'F8.3, 5X,'DS=',F9.3,3X,'MSx2='F12.3,
     6//,4X,'SC = 'F8.3,//,5X,'Z = 'F8.3)
      ENDFILE 6
      END
```

IV. Factor extraction program for HSCL

The following program outputs factor scores on a series of ratings for the following HSCL dimensions:

1. somatization
2. obsessive-compulsive
3. interpersonal sensitivity
4. depression
5. anxiety

(P.T.O)

```
      PROGRAM HSCLFAC
      INTEGER SCORE(13,58),ID,N,I,J
      REAL FLOAD(58),CMPSCR(13,58),FSCORE(13,5),FSUM1,FSUM2
      REAL FSUM3,FSUM4,FSUM5
      FSUM1=7.19
      FSUM2=5.38
      FSUM3=4.44
      FSUM4=5.94
      FSUM5=4.43
      WRITE(1,11)
   11 FORMAT(5X,'SUBJECTS ID?: ')
      READ(1,10)ID
   10 FORMAT(I2)
      WRITE(1,21)
   21 FORMAT(5X,'NO. OF SCALES?: ')
      READ(1,10)N
      CALL OPEN(6,'SCORE   DAT',0)
      DO 1 I=1,N
      READ(6,20)(SCORE(I,J),J=1,58)
   20 FORMAT(58I1)
    1 CONTINUE
      ENDFILE 6
      CALL OPEN(6,'FLOAD   DAT',0)
      READ(6,30)(FLOAD(I),I=1,58)
   30 FORMAT(6(10F4.2,/))
      ENDFILE 6
      CALL OPEN(6,'FSCORE  DAT',0)
      DO 2 I=1,N
      DO 3 J=1,58
    3 CMPSCR(I,J)=SCORE(I,J)*FLOAD(J)
      FSCORE(I,1)=(CMPSCR(I,1)+CMPSCR(I,4)+CMPSCR(I,12)
     6+CMPSCR(I,14)+CMPSCR(I,27)+CMPSCR(I,42)+CMPSCR(I,48)
     6+CMPSCR(I,49)+CMPSCR(I,52)+CMPSCR(I,53)+CMPSCR(I,56)
     6+CMPSCR(I,58))/FSUM1
      FSCORE(I,2)=(CMPSCR(I,9)+CMPSCR(I,10)+CMPSCR(I,28)
     6+CMPSCR(I,38)+CMPSCR(I,45)+CMPSCR(I,46)+CMPSCR(I,51)
     6+CMPSCR(I,55))/FSUM2
      FSCORE(I,3)=(CMPSCR(I,6)+CMPSCR(I,11)+CMPSCR(I,24)
     6+CMPSCR(I,34)+CMPSCR(I,36)+CMPSCR(I,37)+CMPSCR(I,41))
     6/FSUM3
      FSCORE(I,4)=(CMPSCR(I,5)+CMPSCR(I,15)+CMPSCR(I,19)
     6+CMPSCR(I,20)+CMPSCR(I,22)+CMPSCR(I,26)+CMPSCR(I,29)
     6+CMPSCR(I,30)+CMPSCR(I,31)+CMPSCR(I,32)+CMPSCR(I,54))
     6/FSUM4
      FSCORE(I,5)=(CMPSCR(I,2)+CMPSCR(I,17)+CMPSCR(I,23)
     6+CMPSCR(I,33)+CMPSCR(I,39)+CMPSCR(I,50)+CMPSCR(I,57))
     6/FSUM5
    2 CONTINUE
      WRITE(6,31)ID
   31 FORMAT(5X,'SUBJECT NO: ',I2)
      DO 4 J=1,5
      WRITE(6,41)J
   41 FORMAT(/,5X,'FACTOR',I1)
      WRITE(6,51)(FSCORE(I,J),I=1,N)
   51 FORMAT(10F5.2,/3F5.2)
    4 CONTINUE
      ENDFILE 6
      END
```

APPENDIX C

EXPERIMENTAL SUBSTANCES

I. SOURCE OF INGESTABLE MATERIALS

Tryptophan used in the present study was obtained from Healtheries of New Zealand Ltd. The quantities required for the present investigation were supplied in the form of 500mg tablets. Healtheries also supplied placebo in the same sized tablet form. There was a slight colour coat difference between the respective substances.

II. SPECIFICATIONS OF TRYPTOPHAN USED IN THE PRESENT STUDY

The certificate of analysis accompanying delivery of tryptophan used in the present investigation contained the following information:

purity	99.4%
appearance	white crystalline powder
odor	none
PH (% solution)	5.7%
specific rotation $[\alpha]_D^{20}$	-30.6%
appearance after resolution	clear
chloride (Cl)	less than 0.02%
sulfate (SO_4)	less than 0.02%
ammonium (Nh_4)	less than 0.02%
heavy metal (as Pb)	less than 10ppm
iron	less than 30ppm
arsenic (AS_2O_3)	less than 1ppm
other amino acid	not detected
loss on drying	0.06%
residue on ignition	0.02%

III. PLACEBO COMPOSITION

Placebos were composed of the physiologically inert compound: dicalcium phosphate dihydrate with traces of micro-crystalline cellulose.